VOLUME 58 • JULY 1957 • NUMBER 1

A.M.A. ARCHIVES OF OPHTHALMOLOGY

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Studies on Ocular Blood Flow in the Rabbit
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The Effect of Age upon Lens Metabolism
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Visual Field Defects Due to Optic Nerve Compression by Mass Lesions
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Bilateral Papilledema in Otherwise Well Patients
M. Wallace Friedman

Further Studies on the Incidence of Antibiotic-Producing Micro-Organisms of the Ocular Flora
Seymour P. Halbert, D. Locatcher-Khorazo, C. Sonn-Kazar and L. Swick

Preganglionic Cervical Sympathectomy and Aqueous Flow
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Nonspecific Granuloma of Lacrimal Sac Harboring Polyethylene Tube
Sprinza Weizenblatt

New Scissors for Cataract Extraction
Harold G. Scheie

Strabismus
Marshall M. Parks

News and Comment

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Our primary purpose in this illustration is not simply to solve the optical problems of an occasional middle-aged plumber, but to illustrate that with a little ingenuity a segment of any size, shape, and prismatic effect can be ground or fused to any lens. Keeping this in mind, the conscientious optician can provide the answer to many ophthalmic problems insoluble with commercially available lenses.

"if it's a lens problem, let's look at it together"

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Published monthly by the AMERICAN MEDICAL ASSOCIATION. Editorial and Circulation Offices: 535 North Dearborn Street, Chicago 10, Illinois. Publication Office: Thompson Lane, Box 539, Nashville 1, Tennessee. Change of Address: Notice to the circulation office should state whether or not change is permanent and should include the old address. Six weeks' notice is required to effect a change of address. Second-class mail privileges authorized at Nashville, Tenn., Aug. 6, 1956.

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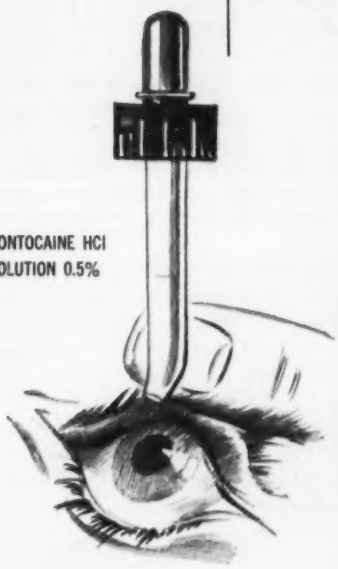

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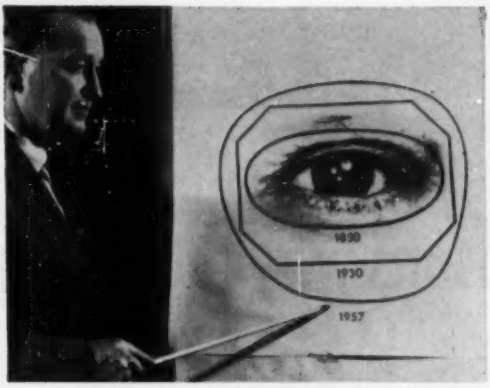

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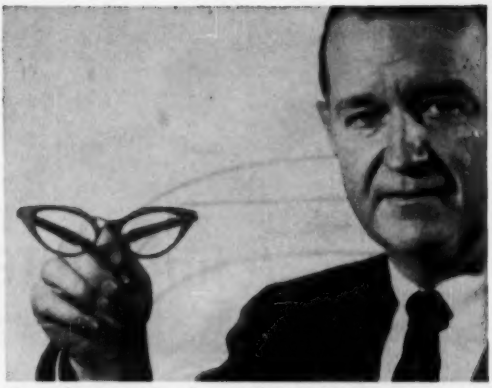

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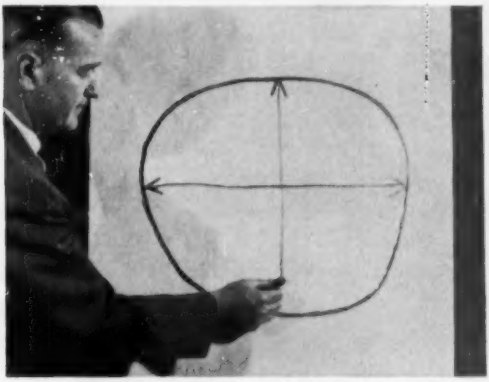

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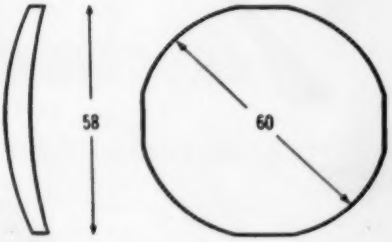

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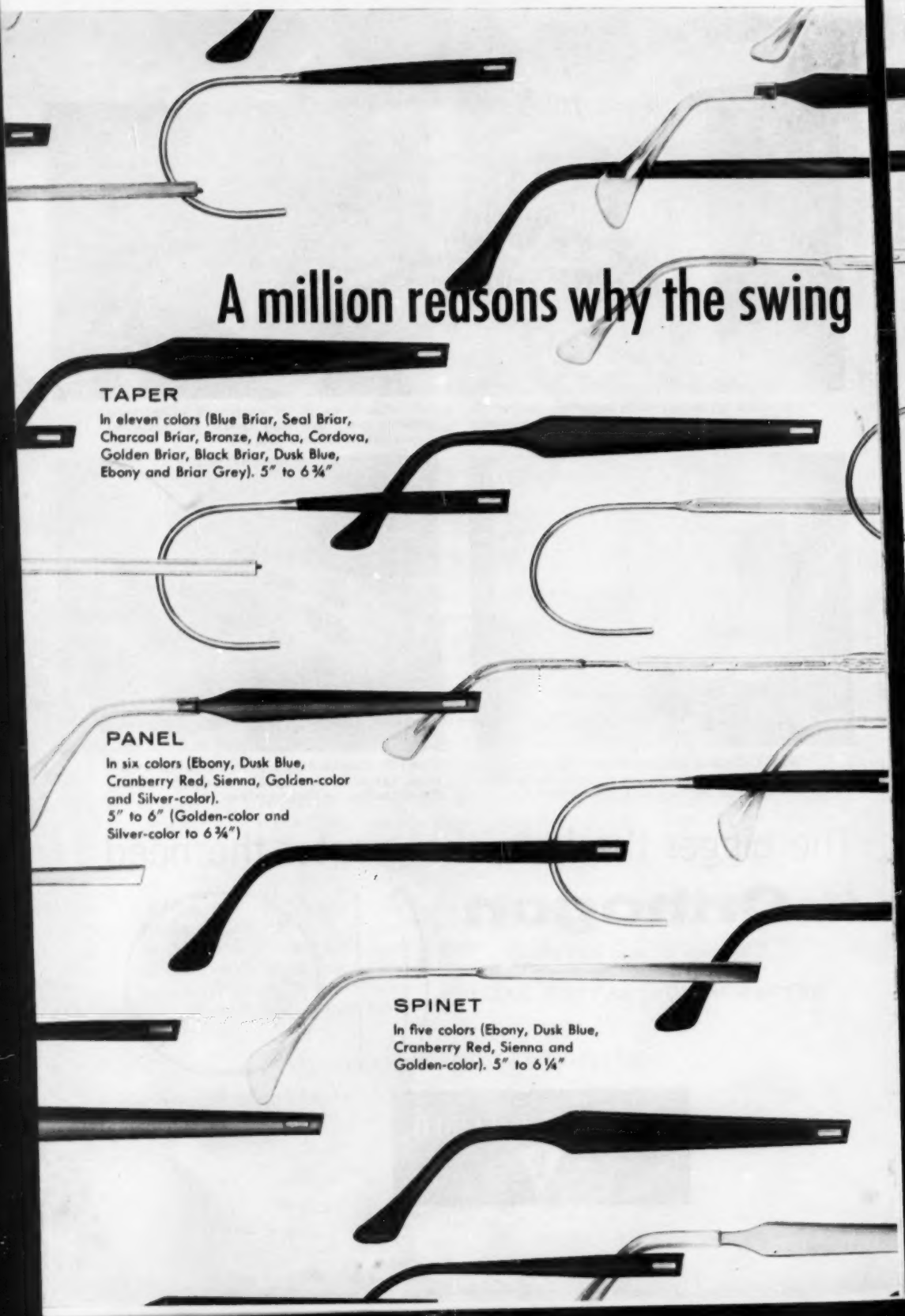
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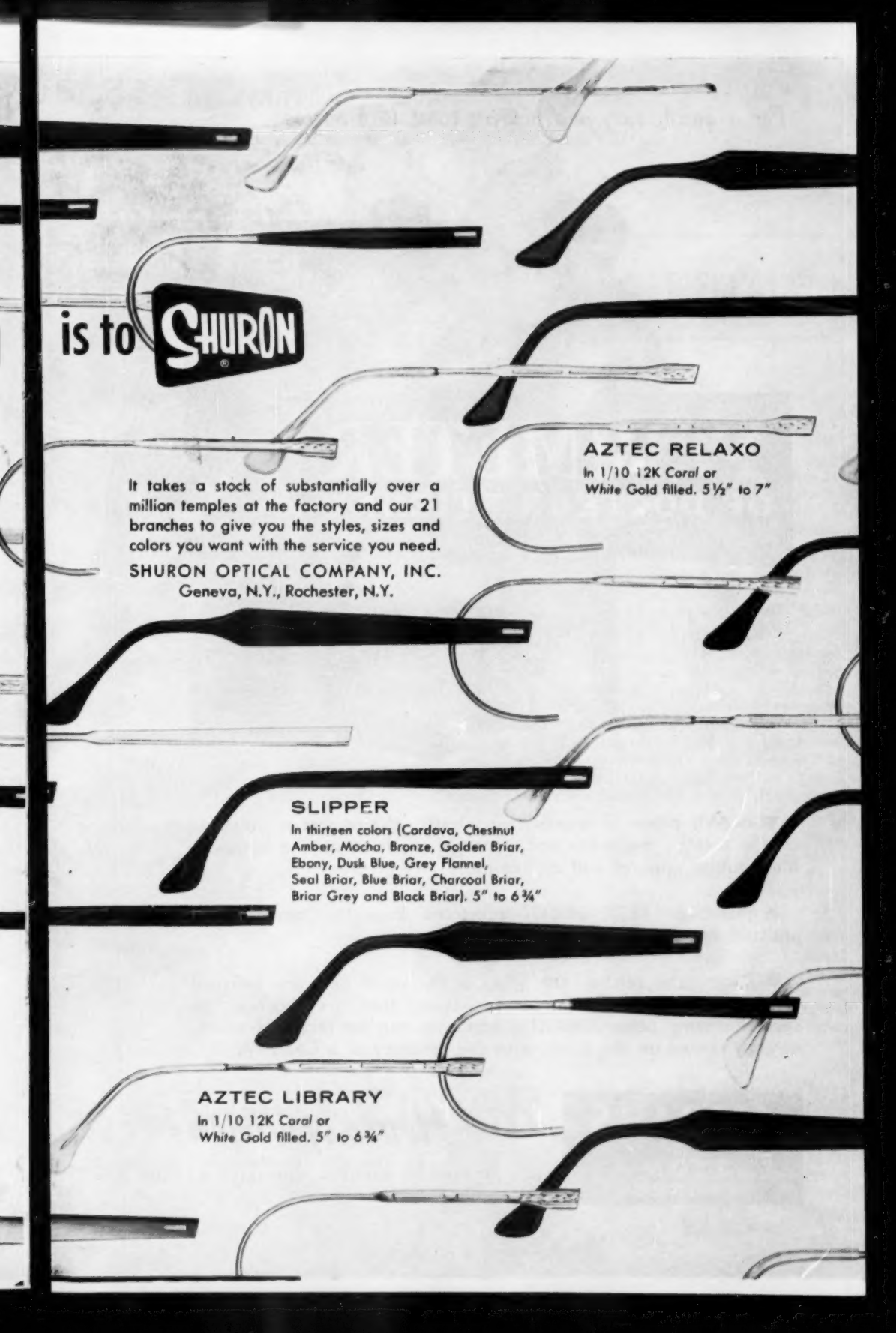
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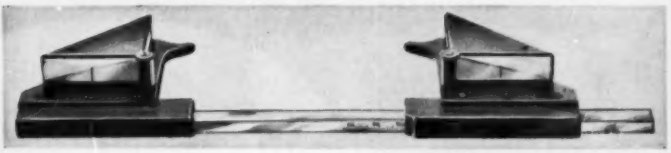

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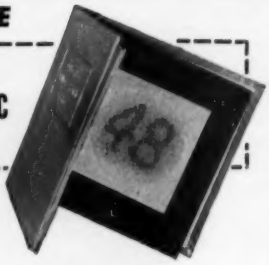

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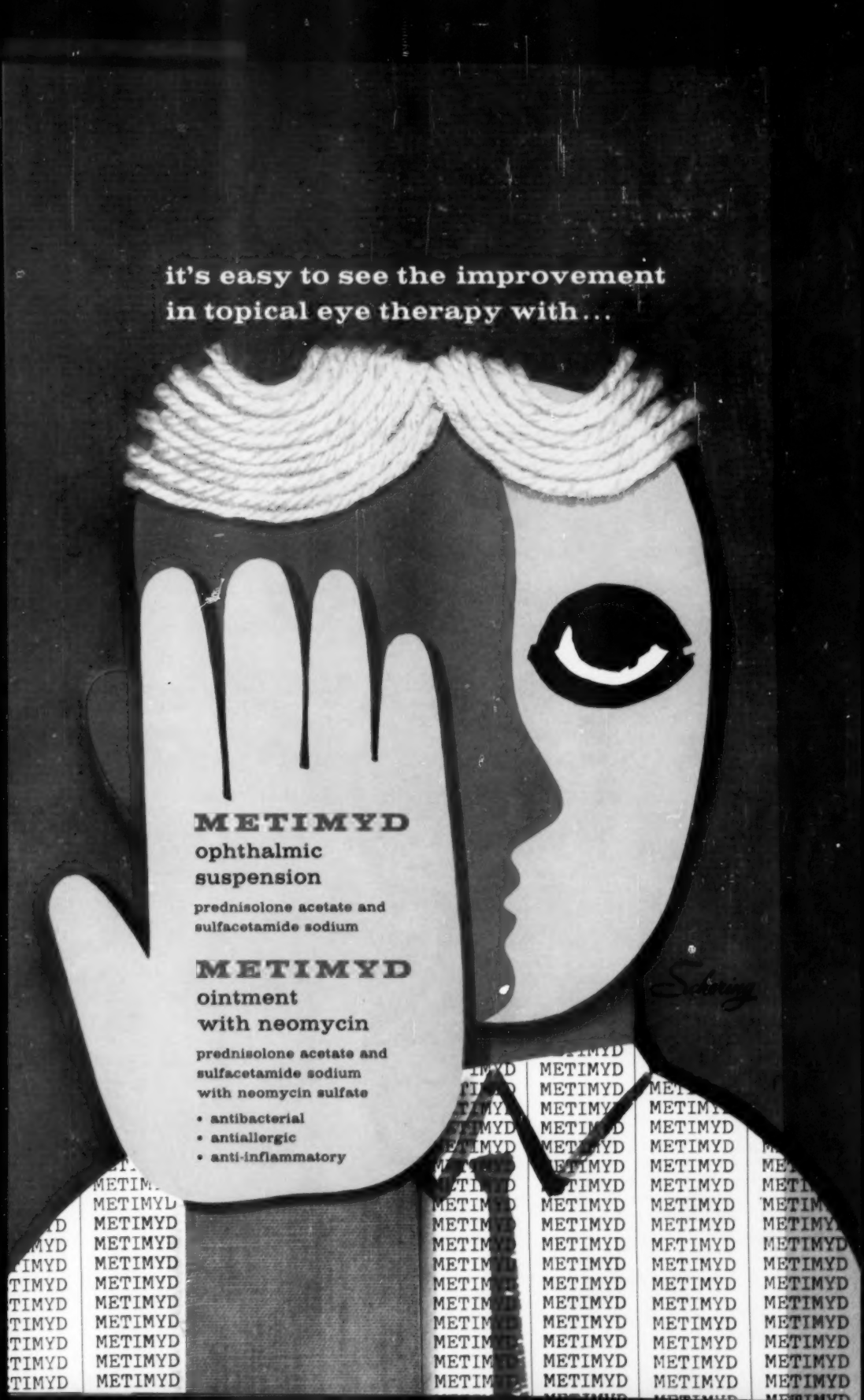

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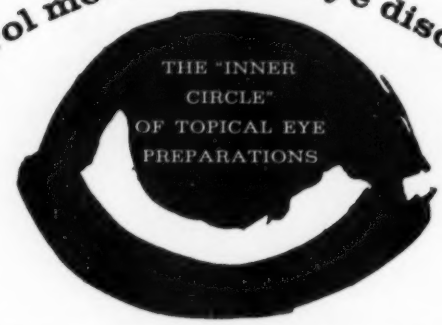

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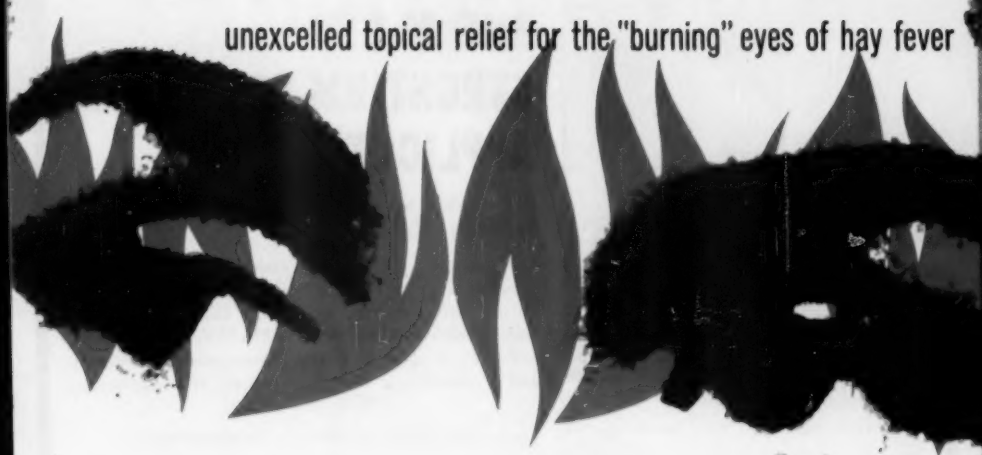

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Central Serous Choroidosis Associated with Amebiasis

A Record of Nine Cases

ALSON E. BRALEY, M.D., and HENRY E. HAMILTON, M.D., Iowa City

Introduction

Loss of central visual acuity is disturbing to the patient and to the ophthalmologist. Disturbance of the central vision may be associated with central choroiditis or with retinitis. It is commonly a progressive disease which fails to respond to any specific therapy, and the result is a central scotoma. The ophthalmologist frequently makes desperate efforts to treat the lesion either as choroiditis or as a vascular disease of the retina.

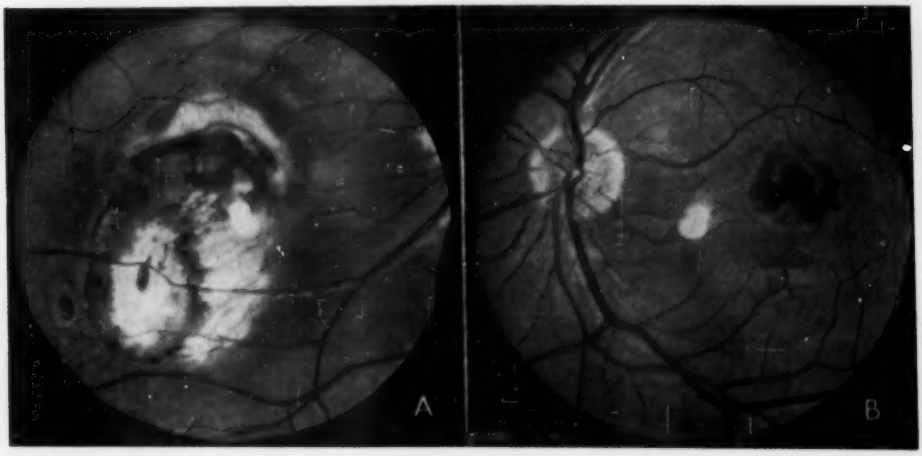
There have been many descriptive terms applied to these central lesions, and occasionally these central lesions are very characteristic. Toxoplasmosis of the retina and choroid is now a recognized clinical entity which can be supported by laboratory and x-ray findings (Fig. 1*a*.). Since these lesions in the macula are almost always progressive and result in considerable visual disturbance, early clinical and laboratory diagnosis and prompt treatment may result in some saving of vision.

Received for publication Jan. 30, 1957.

A major portion of this paper was presented by Dr. Braley before the College of Physicians, Philadelphia, Nov. 14, 1956, for the George B. De Schweinitz Lectureship.

Head and Professor, Department of Ophthalmology (Dr. Braley), and Associate Professor, Department of Internal Medicine (Dr. Hamilton), State University of Iowa University Hospitals.

Fig. 1.—*A*, toxoplasmosis; *B*, amebiasis.



We should like to describe a group of patients, nine in all, with macular lesions that we think are clinically characteristic. In six of these patients the clinical picture of the macular lesion eventually led to the diagnosis of amebiasis, and in three, to presumptive diagnosis of amebiasis. The lesion is characterized by what appears to be a cystic area almost always in or near the fovea associated with hemorrhages under and into the retina or between the choroid and retina. (Fig. 1*B*). The vitreous is slightly detached over these lesions, and there are opacities in this detached area. The pigment epithelium becomes hyperplastic around the cystic area. These patients have been followed for varying periods from one to seven years. All of these patients were treated initially with antiamebic drugs such as diiodohydroxyquin (Diodoquin), chloroquine, and carbarsone. The response to treatment was usually prompt, and some of the macular lesions healed rapidly; others improved considerably, while others were followed during treatment and then treatment was discontinued and the lesion was allowed to re-form, after which treatment was resumed, with regression of the lesions. These nine patients were compared with the patients with other types of macular lesions, some of which were probably due to toxoplasmosis while others were probably senile macular degenerations.

Because of the apparent reversibility of this particular lesion associated with amebiasis, it is important for the ophthalmologist, the internist, and the parasitologist to work together with all these patients who have pigmented cystic lesions in the macula. Since the ophthalmologist is usually the first to see these patients, he should be aware of this type of lesion and should request the help of the internist to search for evidence of amebiasis and subsequently direct specific antiamebic therapy. This paper is presented to acquaint ophthalmologists with the clinical diagnosis of central serous choroidosis associated with amebiasis.

Clinical Material

All patients in this study were examined for clinical evidence of amebiasis, other infectious disease, or a metabolic disorder. Hemograms including hemoglobin, white blood cell count, differential blood cell count, and erythrocyte sedimentation rate were found to be normal unless otherwise indicated. Urinalysis was negative in each case for albumin, blood, sugar, or abnormal sediment. Serological tests for syphilis and brucellosis were negative, and tests of the serum in the more recently studied cases were negative for the lupus erythematosus-cell phenomenon. The chest x-ray studies showed healthy chest, with no evidence of healed histoplasmosis or active or inactive tuberculosis. The stools were obtained for parasitological studies by direct aspiration of the material from the sigmoidoscope and from purged stool specimens. The fresh stools were examined directly for trophozoites. Stools obtained from the purges were placed in polyvinyl alcohol preservative and examined after staining for amebae and other parasites. Solid stool specimens were studied by the flotation methods for ova and cysts. Each patient was sigmoidoscoped in a search for evidence of bowel wall changes compatible with amebiasis. The complement-fixation tests were carried out by the Communicable Disease Center Laboratory when that test was available as well as with antigens supplied by Eli Lilly & Company.

A positive diagnosis of amebiasis was established by finding the parasite Endamoeba histolytica in six of the nine patients discussed. A presumptive and most likely diagnosis was made in the remainder on the basis of clinical history; the presence of clinical signs of disease, such as the presence of a tender liver and coppery color of the skin, and/or sigmoid colon changes seen in amebiasis, coupled with a positive complement-fixation test for amebiasis and a rapid recovery from the clinical illness following antiamebic therapy. The drugs used in therapy are practically specific for

amebiasis with the exception of malaria and lupus erythematosus. These two illnesses were excluded as possible causes of the patient's disability.

The patients were treated with repeated courses of therapy, with use of diiodohydroxyquin U. S. P. 615 mg. three times a day for 20 days, combined with 0.5 gm. of chloroquine at bedtime for 20 days. Subsequent courses ordinarily consisted of 0.25 gm. of carbarsone U. S. P. three times a day combined with 0.5 gm. of chloroquine phosphate U. S. P. at bedtime for 10 days. This was followed after an appropriate rest period with another course of diiodohydroxyquin and chloroquine.[1,2] A minimum of three courses of therapy was given, after which time stools were studied once more for parasites and also an evaluation of the clinical state was made, giving consideration to the sense of well-being, bowel function, weight gain, presence or absence of liver tenderness, and an evaluation of the eye lesion. Fumagillin was used in conjunction with the above drugs on occasion; however, it was used only after the eye lesion had improved or become inactive. Each patient was started on antiamebic therapy when the eye lesion was active, and during the subsequent months no other medications were used. Other antibiotics and sulfanilamide drugs were excluded from the therapy of the amebiasis. Some patients had had chlortetracycline (Aureomycin), oxytetracycline (Terramycin), or penicillin prior to this study; however, such therapy had not made the slightest alteration in the course of the macular disease.

In the presentation of the cases the general background and course of the illnesses are followed by a detailed description of the eye lesions.

CASE 1.—A 34-year-old man was first seen in January, 1949, complaining of blurred vision in the left eye with a gradual onset 12 days previously and a slight impairment of visual acuity in the right eye. A macular lesion in the left eye was described at that time. In the intervening years, the patient was observed and treated with histamine, tonsillectomy, rutin, cortisone, and antibiotics, with no improvement. In 1953 he was restudied for a generalized disease and amebiasis. He had enjoyed good health prior to 17 months' tour of military duty in New Guinea, 1944-1945. In 1945-1947 he had three episodes of shaking, chills, and fever but attempts to demonstrate the presence of malaria parasites were negative. In 1947 to 1949 he had intermittent low-grade fever lasting four to five days and never really felt well. He had changes in bowel habits, with a few days of constipation, then a few days of normal bowel movements, and this would be followed by frequency of stool for several days. His skin was sallow. There was upper abdominal tenderness to palpation. Sigmoidoscopic examination revealed clusters of small ulcerations on the rectal valves, and the fresh stool specimen revealed trophozoites characteristic of E. histolytica. In addition, Chilomastix mesnili organisms were found by direct examination and in a PVA-preserved specimen stained by iron and hematoxylin techniques. The complement-fixation test for amebiasis was positive, and it became negative after therapy for amebiasis. Studies for infectious mononucleosis and serological tests for typhoid, paratyphoid, brucellosis, and syphilis were negative. Special surveys of the gastrointestinal tract, intravenous pyelograms, and studies of the ear, nose, and throat for evidence of paranasal sinus disease were all negative. The patient was treated intensively with several courses of diiodohydroxyquin, chloroquine, and carbarsone in varying combinations. The signs and symptoms and laboratory evidence of amebiasis disappeared, and the macular lesions became quiescent, as described below. The patient was asymptomatic in Spring, 1956.

The course of the eye lesions is described in detail as follows: When the patient was first seen, on Jan. 25, 1949 (Fig. 2*A*), because of blurring of vision in the left eye, the corrected vision in the right eye was

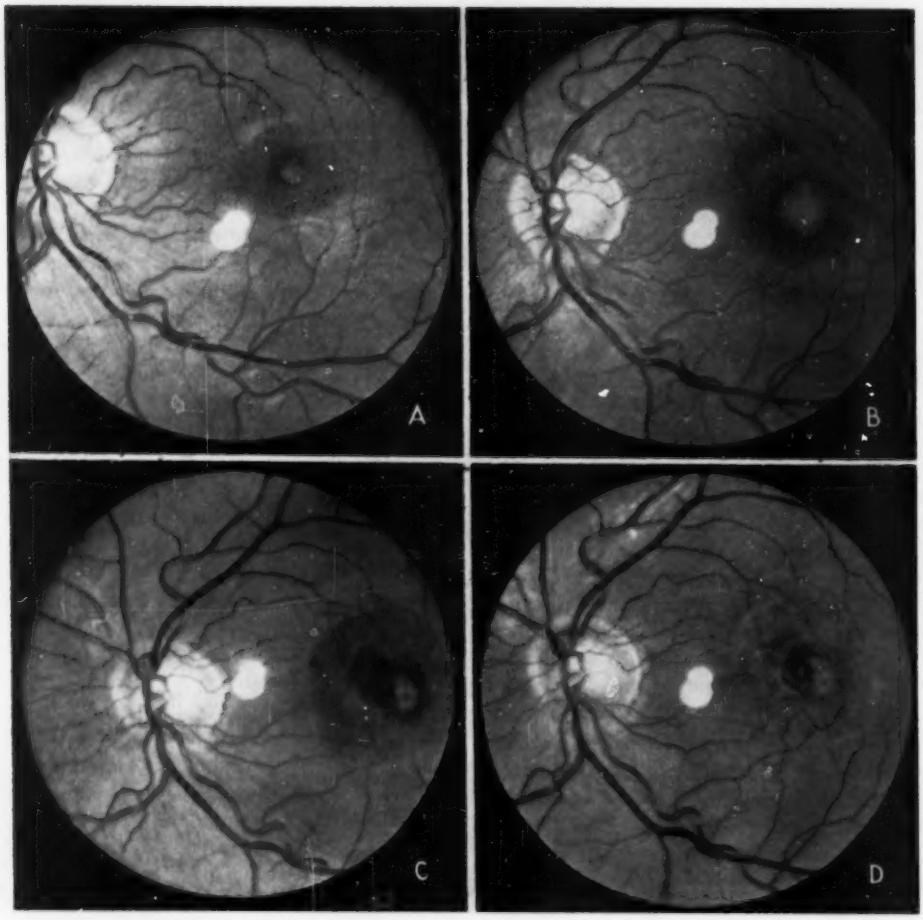


Fig. 2 (Case 1).—*A*, 1949; *B*, 1950; *C*, 1953, corticotropin; *D*, 1954, after amebiasis therapy.

6/3−4, and in the left eye 6/6. In the macula of the left eye was a light-colored mottled oval slightly elevated area which appeared to be at the fovea. The impression was that the lesion in the eye was an inactive chorioretinitis. Field examination showed a tiny central scotoma for the 1 mm. red target at 1200 mm. The central lesion by August, 1949, began to show some pigmentation, and vision in the left eye had gradually receded to 6/9−1. (Fig. 2*B*). When he was seen, in April, 1953, vision in the left eye had gradually failed and it was worse than it had been at any other time. On examination, vision in the left eye corrected was 6/12−3. There was a pigmented lesion in the macula, with some evidence of active inflammation, which appeared to be slightly parafoveal. There was some edema, with a cystic area near the fovea. The biomicroscope revealed a few fine floaters between the anterior surface of the lesion and the posterior surface of the vitreous. He was given corticotropin (ACTH), but in spite of this treatment vision continued to deteriorate in the left eye and for the first time the patient began having symptoms in the right eye (Fig. 2*C*). He stated that the symptoms in the right eye began just as they had begun in the

left eye, reducing his vision to 6/6 from 6/3. On the corticotropin treatment many hemorrhages developed and there were numerous infiltrates around the macular area. The central scotoma became larger. In September, after repeated examinations that had been previously conducted for focal infection, examination of his stool was positive for E. histolytica. He was given 10 days of therapy with chloroquine, 0.25 gm., and carbarsone, 0.25 gm., for 10 days. During treatment with chloroquine and carbarsone the cyst in the macula nearly disappeared. By November, 1953, the vision in the right eye had improved to 6/3; however, the lesion in the left eye was still active but there was less of a cyst in the macula. There were many hemorrhages and some edema still present. The patient was treated with diiodohydroxyquin and chloroquine for 20 days. On this treatment he seemed to improve again, but in December amebae were again found in the stools. In December, 1953, he was again treated for two weeks. From the first, he demonstrated some improvement in vision in the left eye, without any further deterioration in the right eye. From April, 1954, until October, 1954, he did not receive any treatment.

When he was seen on Oct. 5, 1954, vision in the right eye was 6/6 and was slightly blurred. There was a tiny cyst in the fovea. He was again treated for a two-week period, and the cyst disappeared (Fig. 2*D*). During 1955 he still had occasional bouts of fever and it seemed that each time he would get some flare-up in the eye. Treatment was continued periodically. In August, 1955, he had no fever and seemed to be entirely well. The vision in the right eye returned to 6/3, and the vision in the left eye began to improve. He was again treated with chloroquine and carbarsone before each meal. This time treatment was continued for 20 days. Vision in the left eye has gradually improved to 6/21, and no amebae are now present in the stool.

CASE 2.—A woman was first seen when she was 26 years of age, in 1946, because of decreased vision in the left eye which had begun a few months previously. At that time, a pigmented cystic lesion was observed in the macular region. She was again seen in January, 1951, and was admitted to the hospital two weeks after an acute febrile illness associated with migratory redness and swelling of the joints. She had had rheumatic fever at the ages of 12, 13, and 22 years. (On this admission, she was thought to have acute rheumatic fever on the basis of the history, enlarged heart, erythrocyte sedimentation rate of 105 mm. fall in an hour, increased P-R interval in the electrocardiogram, and negative blood cultures. Culture from an open wound on the hand revealed β-hemolytic streptococci. During this acute illness, it was thought that she had a central serous choroidosis which could well be due to amebiasis. It was ascertained that the patient had developed severe and prolonged diarrhea in 1943 when living under conditions of poor sanitation while following her husband in the army. In the intervening years she had had episodic bouts of diarrhea lasting many days. A search for amebae was made; however, none were found, probably because she had been treated with large doses of penicillin and chlortetracycline for her recent febrile illness.) She made a symptomatic recovery from the rheumatic state and was found to have a minimal residual mitral and aortic valve stenosis. In January, 1953, she was admitted for study because of persistence of diarrhea of four to six months' duration. At that time, the stool was positive for the trophozoites of E. histolytica. The sigmoid colon revealed a nonspecific colitis. Vision was further impaired. Three courses of antiamebic therapy were given, with clearing of the signs and symptoms of the amebiasis. The course of the eye lesions is described in detail as follows.

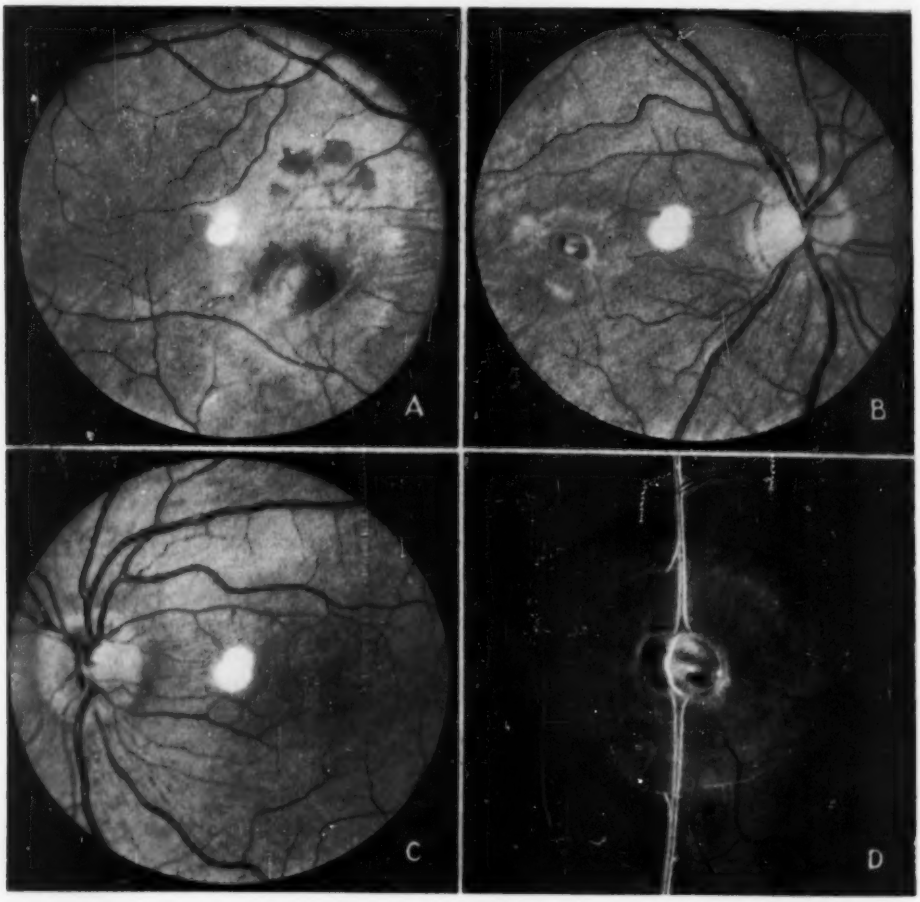
When the patient was first seen by Dr. O'Brien, in 1946, the vision in the left eye was reduced to 6/60 and there was a central scotoma. This was a pigmented lesion with a whitish cystic center. Dr. O'Brien ap-

parently considered the lesion to be either chorioretinitis, central serous choroidosis, or beginning disciform degeneration of the macula. Since there were no vascular changes and no signs of inflammation, he considered the lesion to be a disciform degeneration of the macula. The vision in the right eye was 6/6.

The patient was first seen by one of us in 1951, at which time she had loss of vision in the right eye. The vision in the right eye was reduced to 6/21. There was a small cystic area in the fovea which was surrounded by pigmentary changes and a number of small hemorrhages (Fig. 3*A*). With the biomicroscope and corneal contact lens fine deposits could be seen between the vitreous and the anterior surface of the retina. The cyst in the fovea was clear but appeared to contain an albuminous material. Treatment with diiodohydroxyquin and chloroquine with carbarsone was satisfactory. The response to treatment was prompt, with some healing of the macular lesion. Improvement in vision has been sustained for several years with no recurrence of activity of the lesion.

Case 3.—A 30-year-old woman was admitted to the ophthalmology clinic in 1955 complaining of blurring of vision in the

Fig. 3.—*A*, Case 2; *B*, Case 3, O. D.; *C*, Case 3, O. S.; *D*, Case 3, slit-lamp drawing of macula, O. D.



right eye to the extent that she could no longer read with this eye, double vision, and some blurring of vision in the left eye. The symptoms referrable to the eye were of a few weeks' duration. In 1950 the patient had developed severe bloody diarrhea and after several weeks she had been hospitalized in her local hospital. Treatment with antibiotics brought about improvement; however, she continued to have recurrent diarrhea. On admission to this hospital, in 1955, the ophthalmologic examination revealed a large round darkly pigmented spot in the center of the macula with surrounding deep hemorrhage in the right eye and early pigment changes in the macula of the left eye. The clinical impression was that of central serous choroidosis. Parasitological studies revealed active trophozoites of E. histolytica in the stool. The sigmoidoscopic examination revealed local areas of colitis, normal intravening mucosa, and occasional 0.5 to 1 mm. ulceration characteristic of amebic colitis. She was treated with four alternating courses of combined therapy with diiodohydroxyquin, chloroquine, and carbarsone, and the last course was fumagillin and chloroquine with carbarsone. Following the initial courses of therapy, there was no further progress of the eye lesion and healing of the cystic areas took place. The colitis also disappeared, and sigmoidoscopic and clinical evidence of amebiasis disappeared. In Spring, 1956, examination of the stool was positive for Dientamoeba fragilis. The patient was asymptomatic. Additional courses of diiodohydroxyquin and chloroquine were given. In October, 1956, the macular lesion remained healed. The patient was asymptomatic, and the stools were negative.

Details of the macular lesion are as follows: The vision in the right eye was 6/21, and the vision in the left eye was 6/6. There was a cyst in the right fovea which was surrounded by deep pigmentation. (Fig. 3*B*). There were several deep hemorrhages around this area. The entire macula appeared somewhat edematous. The left eye showed a tiny cyst in the fovea, with slight pigmentation around this area (Fig. 3*C*). The patient was treated, and on Sept. 8, 1955, the vision in the right eye was still 6/21 but the vision in the left eye had improved to 6/4.5. She was last seen on Oct. 5, 1956, and both lesions appeared to be completely healed.

CASE 4.—A 48-year-old woman entered the ophthalmological clinic in August, 1954, with blurred vision in the right eye of three months' duration. The central cyst in the macular lesion was associated with hemorrhage along its margin, pigmentation, and elevation adjudged as viewed with the Hruby lens. This was thought to be characteristic of central serous choroidosis suggestive of amebiasis. A small localized coarsening of bronchovascular markings was found in the right lung field. Serial x-rays of the lung led the radiologist to report that the lesion was stationary and without clinical significance. Search for tuberculosis, including skin tests, gastric washings, and cultures and injection into guinea pigs, was negative. The patient had no bowel symptoms other than constipation. The liver was tender to palpation. Each of three purged stool specimens revealed trophozoites of E. histolytica. The patient received three courses of antiamebic therapy in the next few weeks. In addition, cortisone drops were used in the eye. In January, 1955, the lesions of the eye had progressed and the central hemorrhages were somewhat larger. Cortisone was continued, and by May, 1955, the lesions appeared to be more active. In January, 1956, the lesion was stationary. Further follow-up was not made, and further courses of treatment for amebiasis were not given.

CASE 5.—A 26-year-old man had loss of vision in the right eye of one year's duration. A central pigmented cystic lesion associated with hemorrhage was observed. Stool cultures grew out E. histolytica, and many encysted forms were found on direct stool examination. Antiamebic therapy was instituted. The amebae disappeared from the

stool, and the eye lesion remained stationary. The macular lesion was characterized by a central pigmented lesion associated with hemorrhages mostly in the choroid and subretinal. There was also a small cyst in the middle of this pigmented area. After antiamebic therapy the eye lesion remained stationary.

CASE 6.—A 30-year-old man had decreased vision in the left eye. A macular lesion similar to the one described in Case 5 was found in the left eye, associated with hemorrhage, cystic changes, and pigmentation. Amebae were found in his stool; after antiamebic therapy healing of the macular lesion occurred very promptly and a residual pigment spot was observed when he was last seen, several months after therapy.

Cases 5 and 6 were referred to me (A. E. B.) by Dr. Seneca, at the Eye Institute in New York. Since I came to Iowa, these cases have not been studied further. Their histories and ophthalmological findings are similar to those of the others, and they were my introduction to the disease entity.

CASE 7.—A 27-year-old man, first seen in April, 1953, noted distortion of print in the left eye when reading. He was found to have a macular lesion associated with pigment and hemorrhage. He was treated in succession with nicotinic acid and intravenously by administered corticotropin. By July, 1953, the lesion had progressed, and one of us (A. E. B.) saw this patient and suggested that the macular lesion was a central serous choroidosis associated with amebiasis. It was ascertained that this physician had recently returned from two years of field duty in Korea and for several months had felt unduly fatigued, lost weight, felt generally poorly, and had had anorexia. He appeared chronically ill. The skin presented a decided general mottled coppery appearance similar to the chloasma of pregnancy. The liver was tender to palpation. Many stool examinations, including cultures for amebae, were negative. The sigmoidoscopic examination also was negative. The complement-fixation test for amebiasis was strongly positive. Several courses of antiamebic therapy consisting of diiodohydroxyquin, chloroquine, and carbarsone brought about a complete clinical recovery, with loss of liver tenderness and weight gain of 20 lb. (9 kg.), and several subsequent compliment-fixation tests for amebiasis were negative. As described below, the eye lesion became inactive. In 1956 the patient had remained in good health with improvement of vision.

The characteristics of the eye lesions are as follows: In 1950 the vision in each eye was corrected to 6/6 with a myopic astigmatic correction. In July, 1953, a cyst developed in the fovea of the left eye which was surrounded by some pigment and deep hemorrhage. The vision was reduced to 6/21. On nicotinic acid and intravenously administered corticotropin the vision dropped in this eye to 6/30 and the hemorrhages became more extensive (Fig. 1*B*). Treatment for amebiasis was then started, and vision improved to 6/12. After several flare-ups and incomplete treatment the lesion became quiescent and healed.

CASE 8.—A 20-year-old youth was seen in September, 1953, because of blurred vision in the right eye. A macular lesion was observed. He had been in good general health but had suffered from constipation for several years and in the preceding 12 months had had two explosive bouts of diarrhea. He also gave a history of having easy fatigue and having been underweight for the previous year. The stool studies and sigmoidoscopic examinations were negative for evidence of amebiasis. The complement-fixation test for amebiasis was positive. He was treated with several courses of diiodohydroxyquin, chloroquine, and carbarsone and, later, one combined course of fumagillin and chloroquine. The symptoms of fatigue disappeared some months after therapy was begun; the complement-fixation tests were negative.

The eye lesions were characterized by the following findings: The vision in the left

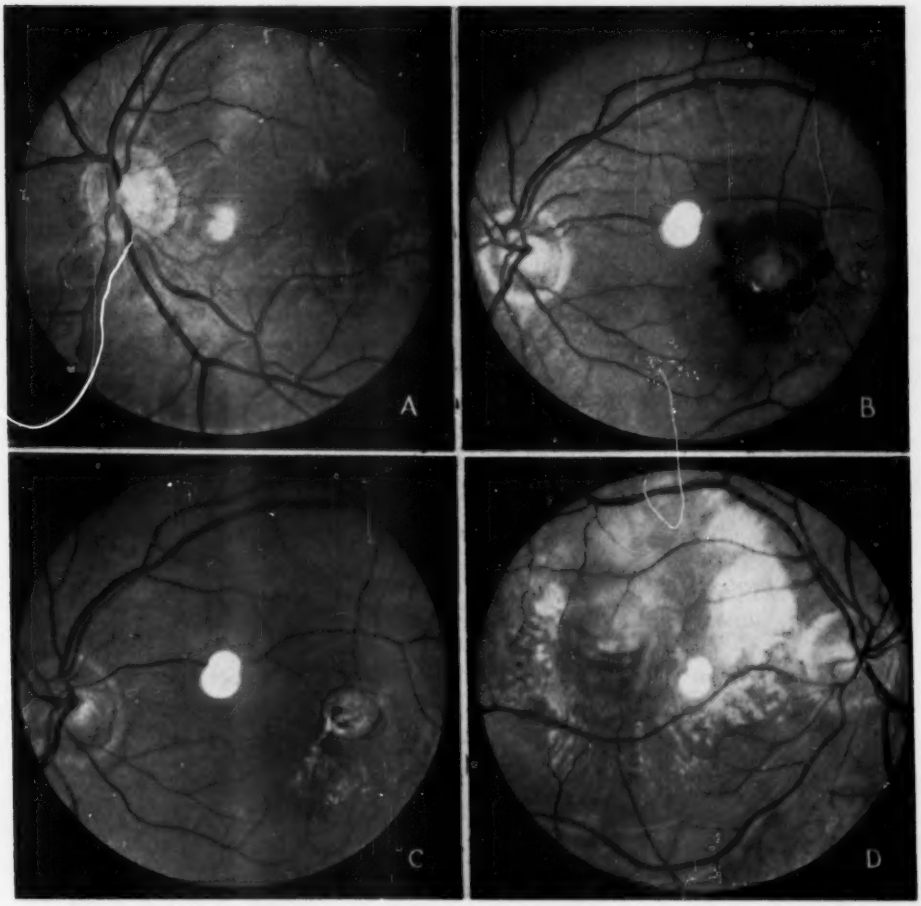


Fig. 4.—*A*, Case 8; *B*, Case 10, possible toxoplasmosis; *C*, Case 10, after pyrimethamine treatment; *D*, Case 11, etiology unknown.

eye was reduced to 6/9, while the vision, corrected, in the right eye was 6/4½. In the macula there was a slightly elevated pigmented lesion near the inferior temporal vein. There were also some pigmented changes in the fovea. Between the macula and the other lesions beneath the superior temporal vein was a small cyst (Fig. 4*A*). The field showed a 2 degree central scotoma in August and December, 1953. The macular lesion became quiescent and healed. In June, 1955, there were no particular complaints of or positive findings other than the healed macular lesion.

CASE 9.—A 55-year-old woman was seen in 1951 in the medical department with a one-year history of right upper abdominal distress, increased amounts of flatus, and undue fatigue. No visual disturbances were noted. The patient was not examined with the ophthalmoscope. The liver was diffusely tender from the xyphoid process to the right lateral costal margin. The skin presented a characteristic mottled coppery pigmentation. The liver-function studies, including determination of total proteins, cholesterol, and esters and thymol-turbidity and zinc-turbidity tests, were normal. Stool studies for parasite and ova were negative. The com-

plement-fixation test for amebiasis was positive. The patient was treated with diiodohydroxyquin and chloroquine. The patient was seen again in 1956, with signs and symptoms of allergic rhinitis of three months' duration, the cause of which was not determined. The patient had no complaints referrable to the abdomen. The liver was nontender at this time, and this organ was not enlarged. The ophthalmoscopic examination revealed an inactive paramacular lesion in the left eye which did not involve the fovea centralis and, therefore, apparently had not impaired the vision.

The lesion had the following characteristics: There was a flat yellowish lesion surrounded by dense pigmentation in the left eye. This lesion was slightly temporal and above the fovea. The lesion was characteristic of a healed lesion.

The following cases had central macular lesions but did not have evidence of amebiasis and did not respond to antiamebic therapy.

CASE 10.—A 35-year-old fat housekeeper was admitted to the ophthalmology service because of failing vision of four months' duration. She also had had a cough productive of about ½ cupful (125 cc.) of sputum daily for many years. There had been no symptoms of bowel disturbance, and her general health had been excellent in her opinion. Bilateral macular lesions were observed. The cheeks presented a "malar flush." There was clubbing of the fingers and toes. The abdomen was normal. The sigmoidoscopic examination was negative. Fresh purged stool specimens were negative for the presence of amebae; however, on one occasion Blastocystis hominus was present and the stained stools preserved in PVA revealed D. fragilis on one occasion. The skin tests for coccidioidomycosis and tuberculosis were negative. The skin test for histoplasmosis was positive. The sputum cultures and guinea pig inoculations were negative for tuberculosis. The bronchograms revealed extensive bilateral saccular bronchiectasis. Several courses of treatment with diiodohydroxyquin, chloroquine, and carbarsone had no demonstrable effect on the eye lesion. In 1956 the dye test for toxoplasmosis was strongly positive. The patient was treated as having a probable case of toxoplasmosis with courses of pyrimethamine (Daraprim), sulfadiazine, and sulfisoxazole (Gantrisin). During therapy with these drugs there was improvement in the macular lesion.

A description of these lesions and their clinical course is as follows: The right eye presented a pigmented cyst in the macula which was surrounded by subretinal and retinal hemorrhages. The vision was reduced to 6/21 but could be improved to 6/15. The left eye showed a much larger cystic area, which was surrounded by a large deep hemorrhage (Fig. 4*B*). There was little pigmentation. There was no change in the appearance of the lesion during antiamebic therapy; however, with administration of pyrimethamine and sulfadiazine the hemorrhages began to absorb and whitish areas developed in the macular region (Fig. 4*C*). Since the Sabin dye test and the skin test for toxoplasmosis were positive and there was a favorable response to pyrimethamine, a presumptive diagnosis of toxoplasmosis was made.

CASE 11.—A 33-year-old man was first seen in April, 1954, with failing vision of the right eye for four years and of the left eye for one year. His general health was good, and his past medical history was noncontributory. There were no complaints referrable to the abdomen or gastrointestinal tract. The physical examination was negative except for the macular lesion. The stool studies for ova and parasites on repeated occasions were negative. The complement-fixation test for amebiasis was negative. A thorough search for other infectious disorders was also negative. Several courses of antiamebic therapy were given, with no apparent effect on the eye lesion. The characteristics of the macular abnormality and their course are described as follows.

The media were clear except for a slight vitreous haze. In the fovea and the surrounding macular area was a large cystic

area. This was surrounded by a slight increase in pigmentation and deep hemorrhages between the retina and choroid. There were also hemorrhages near the cystic area. The entire macula was slightly edematous. The lesion in the right eye was larger than that in the left and showed more signs of inflammation in the choroid. (Fig. 4*D*). The lesion became worse on corticotropin therapy.

Comment

Eight of the nine patients presented here were examined because of loss of central visual acuity. Their vision had been decreasing slowly and progressively, and nearly all of them complained of a scotoma. This scotoma was usually small at first but gradually increased in size until there was considerable loss of central vision. In none of them was there evidence of anterior uveitis. There were no deposits on the posterior surface of the cornea, no floaters in the anterior chamber, and no evidence of vascular congestion of the eyeball. The media from the cornea to the retina were clear and transparent. There were no opacities in the vitreous when viewed with the ophthalmoscope. All had a cyst at or near the fovea. Under ordinary circumstances this cyst would be transparent; however, in a few instances the cyst was a little more opaque than most of the transparent cysts. When viewed with oblique ophthalmoscopic light or with the red free light there appeared to be increased pigmentation around the cyst. This increased pigmentation appeared to be in the pigment epithelium. Hemorrhages adjacent to this area sometimes occur. Hemorrhages were, however, very much commoner after the patient had been given cortisone or corticotropin for a short time. After cortisone or corticotropin therapy hemorrhages seem to develop in the posterior layers of the retina or between the retina and the pigment epithelium.

When the fundus lesion is viewed with the contact lens or the Hruby lens, the posterior face of the vitreous or the anterior limiting membrane of the retina extends forward above the lesion, leaving a small space between the retina and the posterior face of the vitreous. This space sometimes contains a few fine dust-like opacities. When the cysts of the fovea are seen with the contact lens and biomicroscopic lens, they are frequently clear and nearly transparent (Fig. 3*D*). During the acute phase, the posterior wall of the cyst can sometimes be seen through the thin anterior wall. The pigment epithelium posterior to the cyst shows proliferation, which is particularly prominent near the periphery of the cyst. As the disease progresses, the cyst becomes more opaque and the anterior wall becomes denser, so that it is more difficult to see through the cyst wall and the posterior wall of the cyst is not as evident. As the cyst becomes more opaque, hemorrhages are commoner in the surrounding retina but increased proliferation of the pigment epithelium is not the rule. As the area begins to heal, there appears to be some thinning of the cyst and the cyst tends to become flatter and less discrete. This leaves a round area in the fovea which is slightly surrounded by proliferation of the pigment epithelium.

During the early phases of the disease, the ophthalmoscopic picture and the changes seen with the slit-lamp microscope would indicate that the major pathology is in the retina and most frequently at or near the fovea centralis. Although in two patients it was slightly paracentral (Case 4 and Case 7), there do not seem to be any changes visible with the slit-lamp microscope in the underlying choroid, although changes in the pigment epithelium can be seen. These are primarily those of proliferation of the pigment epithelium, with increase in the pigmentation surrounding the cystic area. As the cyst heals, the posterior limiting membrane sometimes undergoes changes and tends to accumulate in a roll near the edge of what once was probably the cystic area. This is best seen in the slit-lamp drawing of Case 3 (Fig. 3*D*). Nearly all of the

cases were seen late in the disease, after there had been considerable visual loss; however, a few were seen early, before central vision was decreased markedly. These are Cases 7, 1, and 8. Some of the cases were bilateral—Cases 2, 1, and 3.

Case 1 is one of the more interesting in this series (Fig. 2C). When the patient was seen in 1953, vision in his left eye, which had been involved in 1949, had become worse and he thought he was having some trouble with his other eye. The right eye was seen to have a tiny cyst in the fovea centralis. This could best be seen by slit-lamp examination of the fundus. There were no hemorrhages and no other evidence of inflammation; however, the lesion in the other eye had become active. At this time, the diagnosis of amebiasis was made and treatment was started. The cyst in the right fovea disappeared entirely, and the lesion in the left eye quieted somewhat (Fig. 2D) He was given diiodohydroxyquin and carbarsone for about 10 days, and vision in the right eye became 6/3 and all evidence of the cyst disappeared. He was not treated for three months but returned for reexamination because of some loss of central vision again in the right eye. Each time treatment was begun, there was a small cyst in his right eye in the fovea and with treatment the cyst disappeared. After several of these repeated bouts the patient was convinced that the lesion would appear and disappear but would disappear only on treatment. During this same time he would have some difficulty with his bowels prior to the time when he would have a flare-up in his eye.

The patient in Case 8, likewise, followed the course of treatment carefully. His lesion fortunately was slightly paramacular, and his vision was a blurred 6/6. Treatment has been carried out periodically each time there was a flare-up in the eye (Fig 4A). The lesion has largely disappeared except for some pigmentary changes. Before a definitive diagnosis could be made in Case 2, acute rheumatic fever associated with Streptococcus infection developed. The patient was, therefore, treated with penicillin and chlortetracycline. Her eyes became worse, particularly the one that had been seen earlier. There were more hemorrhages in the macular region, and the vision was decreased. Likewise, cortisone and corticotropin seemed to make the lesion increase in size. Later Case 2 was proved to have amebiasis.

Central cystic retinitis associated with amebiasis may represent a direct invasion by the parasite of the tissues. Since this cyst forms in the retina, the amebae may be brought to the retina by the blood vessels and the cyst may increase in size with time. These cysts then result from the action of the amebae directly on the tissue. These lesions may be similar to other types of amebic lesions of the liver, bowel, lungs, or brain with minimal tissue reaction. If the amebae invade the retina, producing this retinitis, some eyes may have been removed in the past with the type of lesion here described. Amebae in the tissue should not be too difficult to identify provided the tissue is fixed immediately after removal; however, the parasite does have some of the characteristics of inflammatory cells and, therefore, could be overlooked. We were unable to find any definite report in the literature of amebic retinitis except for that of one of us.[3] If the higher incidence of eosinophilia in amebiasis is taken as evidence of hypersensitivity, it is possible that the lesion in the retina may represent a degree of hypersensitization in the absence of amebae in the macular lesion. The retinitis represents a nonspecific parasite, although we have no direct proof for either hypothesis. We are sure that upon occasion there is an associated chorioretinitis, but the major involvement seems to be in the pigment epithelium and the retina, with very little evidence of choroidal involvement. This helps to make a differential diagnosis between the central retinitis associated with amebiasis and many other types of degenerative and inflammatory lesions of the macula.

Toxoplasmosis of the eye has become an entity which can be suspected by the appearance of the lesion in the fundus.

Toxoplasmosis appears to produce a combination of retinitis and chorioretinitis, with considerable involvement of the pigment epithelium as well. There is considerable pigmentary proliferation in toxoplasmosis without evidence of cystic formation. The lesion of toxoplasmosis appears to be more irregular in shape with more signs of inflammation than are present in the amebic type. While toxoplasmosis may be limited to the central area, it is not uncommon to have other areas of chorioretinitis scattered in the periphery of the fundus. Furthermore, lesions of toxoplasmosis have not responded to antiamebic therapy.

The cystic lesions of the fundus in the nine cases that are described here were single in all but one case. With the slit-lamp examination of the fundus of toxoplasmosis the acute lesions show some thickening of the retina, which is gray but has no evidence of cystic formation. There is marked proliferation of the pigment epithelium and more evidence of chorioretinitis beneath this proliferation of pigment epithelium. There is also other evidence of toxoplasmosis and failure to respond to antiamebic therapy. The skin test for Toxoplasma may be positive and the Sabin dye test may show a reasonably high titer, all of which findings are helpful in making the diagnosis. A case of clinical and laboratory diagnosis of toxoplasmosis is included in this study for comparison with these cases.

Disciform degeneration of the macula may likewise be confusing. Early in disciform degeneration of the macula there appear to be hemorrhages into the pigment epithelium. A whitish membrane seems to form as the hemorrhage becomes organized. The hemorrhages may also be associated with what appears to be drusen in the fundus and on slit-lamp examination; the disc that forms may be elevated in the later stages, but it is rarely cystic. The lesion of disciform degeneration of the macula usually is more widely spread than is the single cystic area of retinitis associated with amebiasis.

The most confusing group of cases are those decribed as central serous choroidosis. In many instances, the lesions of central serous choroidosis and of cystic retinitis associated with amebiasis are almost identical. Both of the lesions are frequently central, near the macula or, at least, paramacular. With the slit lamp there is sometimes a cyst in the central serous choroidosis and sometimes the lesion is more diffuse and irregular in shape. Hemorrhages are frequently prominent in central serous choroidosis, and there are fewer changes in the pigment epithelium. Central serous choroidosis is usually considered to be of vascular origin, but this is difficult to prove, and it may be that some of these cases of so-called central serous choroidosis are actually associated with chronic amebiasis and could respond to antiamebic therapy. It is not our intention to say that central serous choroidosis does not occur, but our main interest is to point out that some of the cases which clinically look like central serous choroidosis are associated with amebiasis and respond to antiamebic therapy. We believe that the ophthalmologist should be acquainted with this condition and should properly refer his patient so that the diagnosis of amebiasis can be made and proper treatment instituted. When the ophthalmologist is not acquainted with the fact that amebiasis of the gastrointestinal tract may be associated with eye lesions, the eye lesion must of necessity progress and eventually heal spontaneously. The ophthalmologist should, therefore, refer these patients with central serous choroidosis to an internist interested in the disease, who will make a diligent search for clinical and laboratory evidence of amebiasis and direct proper treatment. Since the ophthalmologist is using cortisone and corticotropin so widely in the treatment of cases of chorioretinitis and similar diseases, he should, likewise, be acquainted with the fact that cortisone and corticotropin probably will make these lesions considerably worse and tend to cause them to enlarge rather than improve.

Summary and Conclusions

Central serous choroidosis was observed in nine patients with clinically active amebiasis.

The macular lesions responded to intensive courses of antiamebic therapy, with an arrest in progression of the lesions and subsequent healing.

With treatment, vision improved and remained stationary.

Corticotropin and cortisone cause a rapid progression of the macular lesion and should not be used in the treatment of this disorder.

Patients with a macular lesion of obscure etiology should be investigated for evidence of amebiasis.

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The Differential Diagnosis of Retinoblastoma

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I. Introduction

There is no place in ophthalmology where thoroughness is more essential than in the examination of a suspected retinoblastoma, whether it has been discovered in the early stage or after leukokoria has become evident. Completeness of the examination is advisable because the greater extent of the procedures will (1) make a correct diagnosis more likely, (2) increase the confidence of the parents during the catastrophic ordeal, and (3) protect the physician in case he is charged with removing an eye unnecessarily. The last feature is becoming increasingly more important in view of the recent frequency of professional liability suits and the entirely unreasonable size of the awards. A case of this sort would be tailor-made for working on the sympathy of a jury.

This paper, therefore, will stress the modes of examination as much as the differential diagnosis. It is designed to help those of us who see few cases in developing the proper procedures.

The term "pseudoretinoblastoma" or "pseudoglioma" is, of course, a preoperative catch-all diagnosis, for after enucleation the report of the pathologist should make an exact diagnosis possible.

II. Extent of Examination

To aid us in our office in remembering all the steps in this complete examination, we refer to the following outline:

1. Plenty of time for history, examination, discussion, and preparation of armamentarium.
2. Referral of patient to pediatrician for general examination for evidence of metastases, disease, congenital anomalies, and delay of development.
3. Referral for P^{32} readings, where available.
4. Examination, with widely dilated pupils, under general anesthesia, of both eyes by (*a*) ophthalmoscopy, (*b*) measurement of size of corneas, (*c*) hand slit-lamp, (*d*) gonioscopy, (*e*) retinoscopy of both eyes, (*f*) tonometry, (*g*) x-ray of eye for calcium by special technique, and (*h*) transillumination.
5. As many consultants as the parents desire—always one from another office.

All of this information is often very valuable for the better assessment and future care of the case, even if it is not a retinoblastoma. I would stress that, while the child is under an anesthetic, one should get all the data one can.

Obviously, ophthalmoscopy should not be cursory, and one should look for other areas of involvement in both eyes. By using forceps, one can often discover telltale evidence in the periphery, especially in cases showing the ciliary processes.

The size of the cornea often gives a valuable clue, for retinoblastoma occurs almost invariably in eyes that are of a size which is normal for the age of the child.

A hand slit-lamp will help in determining the depth of the opacity, and Tyner has used the gonioscope very effectively to obtain valuable evidence as to details and position of the lesion.

Retinoscopy of both eyes has helped me in understanding the case, for it gives hints as to pathology. The parents often ask about the other eye immediately after the anesthetic, and it is easier for me to do an approximate skiascopy (which is all that is needed) while the patient is asleep than when he is struggling in an office.

While I have had no experience with fluorescin intravenously, it has been of value in differentiating brain tumors and may some day be applicable here.[1]

I always feel much more secure in taking the ocular tension if two certified tonometers

Received for publication March 11, 1957.

which have been checked at frequent intervals are used. (Parenthetically, I believe that every ophthalmologist should always have two such tonometers in his office, to be checked frequently—one against the other.)

Transillumination gives very limited information, but it can be combined at times with profit with ophthalmoscopy. However, it must be stressed that experience has proven that in the differential diagnosis it is almost valueless. A retinoblastoma and almost all pseudoretinoblastomas will transilluminate. Furthermore, there is no evidence that a benign lesion transilluminates and that a malignant lesion does not.

Lastly, I wish to stress the value of several consultations. The questions and presence of the residents in ophthalmology often stimulate one to better effort and thinking.

III. The Armamentarium

One should have in the operating room (1) two major ophthalmoscopes (in case one should cease to work properly), (2) gonioscopy apparatus, (3) hand slit-lamp, (4) two certified tonometers, (5) calipers and ruler, (6) transilluminator, (7) small trial case for retinoscopy, (8) forceps for moving eye, (9) access to radiographic apparatus near by, (10) consultants—and, in a teaching institution, residents, interns, and students.

IV. Appearance and Salient Facts Regarding Retinoblastoma

The textbook facts regarding the appearance of a retinoblastoma may be briefly reviewed. Most important is the statement of Reese[2] that retinoblastoma occurs almost always in a normal-sized eye with a normal anterior chamber. The eye may be larger in the late stage as a result of glaucoma, but an eye which is small for the age of the child almost certainly rules out retinoblastoma. A bilateral case in a premature infant has been reported by Hix,[3] but the small eyes were normal for that age.

The surface of the tumor is usually smooth; the color, particularly in glioma exophytum, is ordinarily yellowish, often with a pink hue. The blood vessels, as in any solid tumor, are of normal color, but they will appear dark in the area of an associated retinal detachment. Many vessels will be seen to dip in and out of the surface; Heath[4] has likened their appearance to that of a porpoise swimming in the water.

The aspect of the calcium deposit has been best described by Reese.[2] "Calcium can be detected in the lesion in almost every case, and its recognition is a most important feature in the diagnosis. The clinical appearance of the calcium varies according to its depth. When it is superficial it has a pearly-white color and is rather sharply demarcated. When it is less superficial, it takes on a white chalky appearance with poorly demarcated borders. When it is dense and superficial, it has the appearance of cottage-cheese."

The vitreous and anterior chamber are normally clear, although daughter cysts may be present. The pupil reacts freely by consensual reaction even in an advanced case.

In most instances, the first evidence of disease to be noted is leukokoria or strabismus, rather than a previous attack of inflammation, as in metastatic endophthalmitis. Most cases are sporadic, but Reese[2] says that a person surviving retinoblastoma is very apt to have children with a like tumor, which is often bilateral. In any case, the history should search for hereditary clues. This feature has been well discussed by Falls[5] and Nicholls.[9]

The lesion is bilateral in about 25% of the cases.

The eye, being of normal size, does not tend to evidence exophthalmos or enophthalmos, as in retrolental fibroplasia. The vision is normal if the lesion is small and not in the macula. The intraocular pressure is normal, even with large tumors, until the iris-lens diaphragm is pushed forward. Visible dentate (ciliary) processes are not

present, and the lens is clear and of normal shape.

The child is almost always normal physically and mentally until metastases occur in the late stage. A few rare cases of spontaneous cures have been reported. Roentgenograms of the eye, if a special and exact technique (Pfeiffer[6]) is used and if the child is under general anesthesia when they are taken, will show calcium in a considerable number of cases. If they have been taken in the customary way, a negative report for calcium is worthless; I have had several cases reported negative for calcium before surgery which showed calcium very plainly in the enucleated eye. Recently I have been taking the picture first, when the patient has just been anesthetized. By the time the other extensive examinations are finished, the film can be ready.

While much work with the radioactive isotopes is in progress, the results, even by the experts, are inconclusive in retinoblastoma and cannot be relied upon at present.

V. Entities That Have Been Confused with Retinoblastoma

These conditions have been confused with retinoblastoma: (*a*) retrolental fibroplasia; (*b*) persistence and hyperplasia of the primary vitreous, persistent tunica vasculosa lentis, encephalo-ophthalmic dysplasia of Krause; (*c*) metastatic endophthalmitis; (*d*) congenital and postnatal retinal detachment, congenital falciform and retinal folds; (*e*) hemorrhage into the vitreous; (*f*) Coats's disease; (*g*) angiomatosis retinae; (*h*) massive retinal fibrosis and exudative retinosis in children; (*i*) congenital cataract; (*j*) congenital anomalies, including coloboma; (*k*) medullated nerve fibers; (*l*) toxoplasmosis; (*m*) brucellosis; (*n*) choroidal sarcoma; (*o*) dictyoma and astrocytoma; (*p*) cysticercosis; (*q*) tuberculosis.

One should be familiar with each of the entities mentioned, but for the sake of simplicity we can divide them into the following categories: (1) other neoplastic entities; (2) inflammatory disturbances, as in Coats's disease and acute retrolental fibroplasia; (3) infections, such as toxoplasmosis and metastatic ophthalmitis; (4) congenital malformations, e. g., congenital retinal detachment, cataract, and persistence of tunica vasculosa lentis or primary vitreous; (5) trauma, as in massive retinal fibrosis or profuse vitreous hemorrhage; (6) nematode infestation.

In the past, the infections, such as meningitis were the commonest cause of confusion in diagnoses; recently, retrolental fibroplasia posed a problem, but in the future congenital malformations will be the commonest pseudogliomas.

VI. Comment

When the ophthalmoscope was invented, it was said that no longer would there be any confusion in diagnosis. Unfortunately, this dream has, as yet, not come true, as evidenced by excellent reports by Bedell[8] and Sanders.[7]

The most difficult decisions will have to be made when the lesions are small, for when an eye is hopelessly involved by any other process and the diagnosis is even slightly in question we are not justified in trying to salvage an eye.

In view of the fact that most of us with an average practice seldom see a retinoblastoma or pseudoretinoblastoma, we ought to have no hesitancy in referring our borderline cases to those who have made a special study of the diagnosis and treatment of these cases. If the parents are hesitant, ask for further consultation and do not insist on precipitous action; most parents will finally acquiesce.

Metropolitan Bldg.

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Studies on Ocular Blood Flow in the Rabbit

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A knowledge of ocular blood flow is of fundamental importance for a complete understanding of the function of the eye in both health and disease. While this fact is well appreciated, investigation of ocular blood flow has been extremely limited. The main reason for this lack of research is no doubt due to the relative inaccessibility and small volume of the vasculature of the eyeball, thus rendering impractical for ocular application most of the usual methods of blood-flow analysis. Perkins [1] and Von Sallmann,[2] using a small thermocouple, measured changes in ciliary blood flow by the determination of temperature changes in that region. Alterations in the electroretinogram [3,4] and flicker fusion frequency [5] have also been utilized as indicators of blood flow changes. Recently, Sapirstein [6] has developed a new technique for the determination of blood flow that seems suitable for a study of ocular blood flow.

Sapirstein states that a foreign substance, after a single intravenous injection, will be distributed initially to the organs in proportion to their blood flow and that for a certain period of time, when the venous drainage is small, the fractional distribution of the foreign substance will parallel the fractional distribution of cardiac output. In order to minimize the venous drainage of a substance during the short time following injection, the substance must be initially rapidly transferred from blood to tissue. Potassium is a suitable substance, and Sapirstein utilized radioactive potassium (K^{42}) on 40 anesthetized adult rats. At various intervals after injection of the isotope he killed the anmials by an intravenous injection of supersaturated potassium chloride and determined the percentage distribution of radioactivity in various organs of the body. The results demonstrated that during the first minute following the isotope injection the fractionation of the radioactivity remained constant, supporting the assumption that during that time the venous drainage of K^{42} was negligible.

Comparing his results with accepted values of blood flow as determined by other methods, he obtained a good agreement for the kidney and fair agreement for all of the other organs studied with the exception of the brain, which showed a poor agreement. In discussing the possible causes of disagreement he mentions species differences and the effect of anesthesia. In the special case of the brain, where his value of 0.1 ml/minute/gram is five times lower than the accepted value, 0.5 ml/minute/gram, he suggests an additional factor. The time interval following the isotope injection when the venous drainage is negligible differs for various organs and depends in part on the ratio of the organ blood flow to the amount of exchangeable potassium present in the organ. A high value of this ratio is associated with a short time interval, and the brain may well exemplify this situation. Thus, Sapirstein's shortest time interval, of five seconds, between injections of isotope and potassium chloride might well have exceeded the time when the venous drainage was negligible. Spurious low values would then be obtained.

Received for publication Feb. 19, 1957.

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This study was supported by the Ophthalmological Foundation through a Gustavus and Louise Pfeiffer Research Foundation Grant-In-Aid and was undertaken by the investigator on a full-time Research Fellowship from the National Council to Combat Blindness.

Method

Unanesthetized male albino rabbits weighing from 2.5 to 3.2 kg., with a mean weight of 2.8 kg., were utilized. Nine rabbits were each injected through the ear vein with 1 cc. of a high-specific-activity K^{42} solution containing approximately 500μ of activity. They were then killed at various intervals by the intracardiac injection of 2 cc. of a supersaturated potassium chloride solution. Death occurred approximately 20 to 25 seconds after the potassium chloride injection. The brain, eyes, and kidneys were immediately removed, drained for a few minutes, rinsed, and weighed. Before weighing, the globes were dissected free of muscle stumps, conjunctiva, and fascia. The mean weights of the brain, both globes, and both kidneys were 8.4 gm., 5.3 gm., and 17.5 gm., respectively. The organs were dissolved separately in a mixture of concentrated hydrochloric and nitric acids, and the radioactivity of an aliquot of each dissolved organ was determined 15 hours later with a scintillation well counter. The radioactivity of the entire organ was then calculated. The total radioactivity of the injected isotope was also determined with the well counter.

A simplified modification of the above technique was then utilized for comparison of the ocular flow of the two eyes in the same rabbit. Paracentesis was done on the right eye of six rabbits 30 minutes before the injection of the isotope, and five additional rabbits served as controls. They were killed as described above but with a fixed time interval of 30 seconds between injections of isotope and potassium chloride. Only the eyes were removed. The radioactivity of each globe was determined by placing the entire globe in the scintillation well counter without first dissolving it in acid.

Results

Table 1 illustrates the organ distribution of radioactivity for the dissolved organs. The time interval is that between the injections of isotope and of potassium chloride. The values differ from those of Sapirstein in that they are all markedly lower. However, the uniform reduction of both kidney and brain values suggests a systematic error. If this is the case, the ratios of the organ values to each other are still valid. While the cause of this large reduction has not been definitely determined, it seems likely that this reduction reflects a loss of isotope to the lungs during the passage of the K^{42} from ear vein to left ventricle. The kidney values, excluding the very low values of Rabbits 1 and 4, show a considerable scatter and yield a mean of 2.2%. As Smith [7] has emphasized the instability of the renal blood flow in the rabbit, the low values for Animals 1 and 4 probably represent a renal blood flow shutdown. The values for the brain show a sudden fourfold drop after the 20-second interval. As this interval in the rabbit might well be equivalent to an interval in the rat shorter than five seconds, these results support Sapirstein's explanation for the observed low isotope fraction in the rat brain. The mean of the first three values for the rabbit brain is 0.13%. There is considerable scatter for the ocular

TABLE 1.—*Distribution of Injected Radioactive Potassium* K^{42}

Animal No.	Time Interval, Sec.	Fractional Distribution of Radioactivity *				
		Kidneys	Brain	Right Eye	Left Eye	Both Eyes
1	10	0.2	0.13	0.06	0.01	0.07
2	20	1.9	0.11	0.02	0.02	0.04
3	20	3.3	0.16	0.02	0.02	0.04
4	30	0.3	0.05	0.01	0.01	0.02
5	45	1.5	0.02	0.01	0.01	0.02
6	45	1.5	0.05	0.01	0.01	0.02
7	60	2.5	0.03	0.01	0.01	0.02
8	180	2.7	0.03	0.05	0.05	0.10
9	300	1.9	0.02	0.01	0.01	0.02

* Expressed as $\frac{\text{organ count}}{\text{total count}} \times 100$.

TABLE 2.—*The Effect of Paracentesis on Ocular Blood Flow*

Experiment				Control			
Animal No.	Left Eye, Counts/Min.	Right Eye,* Counts/Min.	Percentage Difference †	Animal No.	Left Eye, Counts/Min.	Right Eye, Counts/Min.	Percentage Difference
10	1,203	1,805	+ 50	16	3,279	3,178	− 3
11	3,026	7,258	+139	17	1,372	2,165	+58
12	3,567	4,877	+ 37	18	2,377	2,744	+15
13	1,131	3,169	+180	19	2,245	1,910	−15
14	3,916	6,928	+ 77	20	3,400	2,403	−29
15	3,069	5,449	+ 78				
Mean			+ 93				+ 5

* Paracentesis done 30 minutes before isotope injection.

† Calculated by $\left(\frac{\text{counts/min. right eye—counts/min. left eye}}{\text{counts/min. left eye}}\right)\times 100$.

values, although the agreement between pairs is good. The mean total ocular percentage of all values is 0.038%. For equal weights of tissue, the ocular blood flow is 46% of the brain blood flow.

In order to obtain absolute values of blood flow a reference value is required. An absolute value for renal plasma flow can be obtained from the value of the *p*-aminohippuric acid (PAH) clearance. Smith's [7] analysis of 69 clearances on 21 unanesthetized male rabbits done by Brod and Sirota [8] yield a value of 18.2±3.4 cc/kilogram of body weight. With a mean rabbit weight of 2.8 kg. and assuming a 50% hematocrit value, the mean renal blood flow is approximately 100 cc/minute. This value corresponds to the mean kidney isotope fraction of 2.2%. The mean brain fraction of 0.13% then corresponds to a blood flow of 5.9 cc/minute, or a value of 0.70 cc/minute/gram. This is higher than the accepted value, 0.54 cc/minute/gram.[9] The mean total ocular fraction of 0.038% corresponds to a blood flow of 1.7 cc/minute, or 0.32 cc/minute/gram.

Table 2 illustrates the effect of paracentesis on blood flow. The mean difference of 93% for the experiment group is significantly greater than the mean difference of 5% for the control group. Paracentesis thus increases the ocular blood flow by approximately 90%.

Comment

While the mean value of ocular blood flow is only an estimate, the accuracy of the estimate is difficult to evaluate. Further use of this new technique with analysis of results is required for an assessment of its over-all validity and accuracy. As there is a considerable scatter of the data, repetition of the experiment with a larger group of animals is advisable in order to increase the accuracy of the means. In view of the instability of kidney blood flow in the rabbit, the PAH-clearance value, which serves as a reference for calculation of the absolute value of ocular blood flow, may not reflect the true renal blood flow under normal conditions. However, similar factors are operative in the estimate of the kidney isotope fraction, and so any errors will not affect the ratio of the two values. For equal weights of tissue a value for ocular blood flow 46% that of the brain blood flow seems somewhat high, considering the large amount of avascular tissue of the eyeball, although the extreme vascularity of the uveal coat compensates partly.

The modified technique for comparing the blood flow in the two eyes of the same animal is much simpler and less open to criticism. It is noteworthy that the dilation of the ocular vessels that occurs in paracentesis [10] is accompanied by a large increase in the blood flow. An increase in blood flow through a vessel is not always associated with a dilation of the vessel and, according to Poiseuille's law,[11] occurs only if the feeding pressure does not decrease. This is the case in paracentesis but is not necessarily the case after the use of certain vasodilators where a dilation of ocular blood vessels is associated with a drop in general blood pressure.

Conclusion

Sapirstein's fractionation technique for measuring blood flow has been applied to a study of ocular blood flow. Nine rabbits were used, and a mean value of 0.32 cc/minute/gram was obtained, which is 46% of the value obtained for cerebral blood flow. The technique was modified for the comparative study of the blood flow in the two eyes of the same animal. In six rabbits paracentesis of one eye increased the blood flow in that eye by approximately 90%.

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The Effect of Age upon Lens Metabolism

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Perhaps the most common type of ocular ailment resulting in diminution of visual acuity in older persons is senile cataract, a condition characterized by opacification of the normally transparent lens without any direct local or constitutional cause.

The lens occupies a very unique position in the economy of the body. It is entirely self-contained, having neither vascular nor nervous connections, and is surrounded by the aqueous humor, on which it is almost wholly dependent for those processes of metabolic exchange with which its vitality and continuing clarity are so intimately connected. The growth of the lens is normally continuous from early fetal life until somatic death and its crystal clearness is maintained normally.

Many theories have been advanced but relatively little is known concerning the mechanism of pathogenesis of cataract.[1,2] The lens is considered to grow to maturity and then to undergo physicochemical changes associated with senescence. These include changes in permeability of the capsule, chemical composition, metabolic activity, size and weight, etc., which may manifest themselves in alterations of function and visible degenerative disturbances. Our present state of knowledge, however, does not permit us to assign to any of these changes the role of causative or responsible factor in the development of senile cataract.

The lens does no external work in the ordinary sense of the term. Its movement of accommodation is mediated externally by the ciliary body through the suspensory ligaments and not through any innate activity, other than, perhaps, the elasticity of the lens capsule. Nor does it apparently give rise to electrical impulses. Notwithstanding the fact that practically no information is available concerning the metabolic activity of normal human lenses, most investigators and theoreticians in this field favor the concept that the growth, function, and maintenance of transparency of the lens are fundamentally dependent upon the active metabolism of the tissue.

Reports in the literature have suggested that the metabolic activity of the animal lens decreases with increasing weight or age of that organ. Lenses with incipient or advanced cataract show a marked diminution in metabolic activity. Thus, Müller[3] observed that the ability of excised bovine lens to consume glucose from Ringer's solution covered with paraffin decreased with increasing age of the animal. On the basis of the amount of inorganic phosphate disappearing from the medium and the amount of organic phosphate formed by intact excised lenses, cut-up lenses, and cell-free extracts maintained for five hours at 37 C, Süllmann[4] suggested that the ability to metabolize glucose was greater for calf lenses than for beef lenses. Lenses with incipient or advanced cataract showed a marked decrease in the ability to form organic phosphate esters. At about the same time, Müller[5] found that the ability of saline extracts of cattle lens to form alkali-saponifiable phosphate (triosephosphate)

Received for publication Feb. 27, 1957.

A preliminary report of this work appeared in the *American Journal of Ophthalmology* (42: [Oct., Pt. 2] 1956).

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This research was supported by a research grant, B-693(C) from the National Institute of Neurological Diseases and Blindness, of the National Institutes of Health, United States Public Health Service.

from fructose diphosphate decreased with age of the animal. More recently, Nordmann and Mandel[6] reported that the concentration of easily hydrolyzable phosphate (adenosine tri- and diphosphate) and of creatine phosphate in lenses of cattle, rabbits, and rats declined with the age of the species studied. Subsequently, Müller and co-workers[7] found, in agreement with Nordmann and Mandel, that the concentration of seven-minute phosphorus was higher in younger rabbits than in older ones. Müller and Kleifeld[8,9] also found that young rabbit lenses weighing between 200 and 350 mg. when incubated at 37 C with glucose and a buffered solution containing $P^{32}O_4$ incorporated 50% more P^{32} into organic phosphate (seven-minute and difficulty hydrolyzable phosphorus) than did older lenses weighing between 450 and 650 mg. under similar conditions. From these observations it might be inferred that the metabolic activity of the lens, measured in terms of glucolysis, decreases with increasing weight or age of the lens. In this connection, it is important to note that the results and conclusions of the foregoing investigators were based upon the comparative evaluation of equal weights of younger and older lenses. In practically all cases the older lens weighed from 40% to 100% more than the younger lens, and the measured criterion of activity associated with the younger lens was not more than twice as much as that with the older lens. When the results are evaluated in terms of the whole lens, either there is little difference in metabolic activity between the two lens groups or the older lens shows the greater capacity.

With the elucidation of the pathway of anaerobic carbohydrate metabolism in the rabbit lens by Green and co-workers[10] it became possible to study the effect of age upon the individual intermediary reactions. Since metabolism is a regular sequence of enzymatically controlled reactions, a disturbance of any one of these could lead to a slowing-down of or interference with the formation of the end-product, lactic acid, and result in a decrease in over-all metabolic activity of the lens. It was reasonable to expect, therefore, that if such a slowing down of lens metabolism occurred with increased age of the animal, comparative studies with young and old lenses might indicate the point in the sequence of reactions at which the enzymatic mechanism was affected.

Procedure

The lenses were removed immediately after death of the animal, placed in a beaker surrounded by ice, weighed, and frozen by immersing the weighing-vessel in a mixture of dry ice and acetone. For each experiment 12 to 16 lenses were pooled. The young rabbits were killed by cardiac injection of 1-2 ml. veterinary pentobarbital (Nembutal) sodium, and the lenses were removed as previously described.[10] The old rabbits were killed by intravenous injection of air, and the lenses were removed either by the same technique used for young lenses or by an anterior approach after a complete keratectomy and iridectomy. In all cases the lenses were completely freed of adherent ciliary processes, iris, and vitreous body.

The weighed frozen lenses were transferred to a chilled Potter-Elvehjem glass homogenizer equipped with a loosely-fitting smooth pestle and homogenized in sufficient KCl (0.154 M) and $NaHCO_3$ (0.154 M) so that the final mixture, including the water content of the lenses, contained the equivalent of one lens per milliliter. The final pH was between 7.5 and 8.0. The volume of $NaHCO_3$ used was such as to give a final concentration in the incubation mixture of 1.4×10^{-2} M. The H_2O content of the young lenses was 70%, and that of the old lenses 60.3% (Table 1). The frozen old lenses were cut into quarters, and the equivalent of one lens at a time was homogenized with successive additions of the KCl and $NaHCO_3$ until the calculated amount of fluid had been added. The frozen young lenses were homogenized whole, three

or four at a time, in the total fluid volume. The homogenate was centrifuged in an International Refrigerated Centrifuge PR-1 at 0 C for 5-10 minutes at 3000 rpm. From the young lenses a slightly opalescent freely flowing supernatant was readily separated from a small insoluble residue, while with the old lenses a more viscous milky homogenate resulted, in which it was difficult to separate an extract from an insoluble residue. Consequently, with the old lenses the whole homogenate was used.

All incubations were conducted in double side-arm vessels of 15 ml. capacity in a Warburg apparatus at 37 C, initial pH of 7.4 to 7.6, and in a total volume of 1.8 ml. In all cases 1 ml. of extract or homogenate, equivalent to one lens, was present in the center well, and in the hexokinase experiments the enzyme was also present in the center well. The necessary co-factors and other additions were tipped in from the side-arms. All vessels were gassed at room temperature with a mixture of 95% N_2 and 5% CO_2 for 10 minutes and equilibrated in the thermostatic bath for 10 minutes, during which time all glass-stoppered joints were tightened. The side-arm contents were tipped in at zero minutes, the start of the reaction. At the completion of the experiment the flasks were removed immediately and 0.2 ml. 40% trichloroacetic acid was added. The contents of the flasks were diluted to 10 ml. with 5% trichloroacetic acid; the mixture was centrifuged, and the supernatant was analyzed for lactic acid. Controls for the zero-minute values, as well as suitable blanks, were run simultaneously in each experiment.

Materials and Methods

Animals.—The clear crystalline lenses were obtained from pigmented rabbits 3 to 4 weeks old and 3 years old.

Chemicals.—Glucose was Merck's anhydrous, reagent grade. G-6-PO_4·$7H_2O$(Ba),* F-1,6-diPO_4(Ba), and chromatographically pure AMP were purchased from Schwarz Laboratories, Inc. Chromatographically pure disodium ATP was purchased from Pabst Laboratories. $MgCl_2·6H_2O$, Na_2HPO_4 (anhydrous), $NaH_2PO_4·H_2O$, Na_2HAsO_4, $NaHCO_3$, and KCl were analytical reagent grade.

Enzymes.—Hexokinase was a lyophilized powder prepared from autolyzed yeast and purchased from Pabst Laboratories. The enzyme was dissolved in H_2O prior to use.

Analytical Methods.—Lactic acid was determined by the method of Barker and Summerson,[11] as described by Umbreit, Burris, and Stauffer.[12] Protein determinations were conducted by the micro method of Sutherland,[13] with use of Pro-Sol, standardized protein solution of the Standard Scientific Supply Corporation, as a standard.

Solutions of the barium salts of the phosphate esters (G-6-PO_4 and F-1,6-diPO_4) were prepared by precipitating the barium ions in dilute HCl at 0 C with 0.5 M K_2SO_4, neutralizing with dilute NaOH, and removing the $BaSO_4$ by centrifugation and decantation. All solutions were adjusted to pH 7.4.

Total phosphorus was determined by the method of Fiske and Subbarow [14] as modified by Lohmann and Jendrassik,[15] following wet incineration with H_2SO_4-HNO_3 solution. The difference between the total phosphorus content and that before incineration was calculated as the organic P content. Labile phosphorus (7'P) was determined according to the procedure of Lohmann at 100 C and in N HCl.

H_2O content of the lenses was calculated from the loss in weight when the lens was dried in an oven at 110-115 C for two to four hours.

Experimental Procedures

The experiments were designed to determine the conditions under which the maximum amount of lactic acid is produced. All experiments were conducted at 37 C for 60 minutes in 1.4×10^{-2} M $NaHCO_3$ at an

* The following abbreviations have been used: G-6-PO_4, glucose-6-phosphate; F-1,6-diPO_4, fructose-1,6-diphosphate; AMP, adenosine-5-phosphate; ADP, adenosinediphosphate; ATP, adenosinetriphosphate; AsO_4, arsenate.

initial pH of 7.4 and in a gas atmosphere of 95% N_2-5% CO_2. Previous experiences [19] had established that in order to achieve an active glycolyzing system with glucose as substrate it was necessary to fortify the lens extracts with hexokinase and adenosinetriphosphatase, since these two enzymes are deficient in the experimental preparation. In the absence of added adenosinetriphosphatase the incubation mixture must be fortified with inorganic phosphate and with a phosphate acceptor, adenine nucleotide. It had also been shown that AMP was considerably more efficient than ADP as the phosphate acceptor. Consequently, when glucose was used as the substrate the lens extract was fortified with hexokinase, inorganic phosphate, and AMP. With G-6-PO_4 as substrate an active production of lactic acid was obtained in the absence of the added hexokinase, thereby indicating the presence of sufficient quantities of phosphofructokinase in the lens preparation. With this substrate, therefore, only inorganic phosphate and AMP were added. Similarly, with FDP as substrate it was only necessary to add inorganic phosphate and AMP. Because of the general requirement of Mg^{++} in transphosphorylating systems, the effect of added Mg^{++} was evaluated with glucose as the substrate. Although the extract showed no absolute requirement for added Mg^{++} (Tables 2 and 3) but only a slight relative need, the metal ions were nevertheless added. In all cases the concentration of inorganic phosphate added was sufficient to give a theoretical quantitative conversion of the substrate to lactic acid, and optimal conditions were found to be essentially dependent upon the ratio of phosphate acceptor to substrate, other things being constant.

Results

Analytical Data of Lens Groups (Table 1).—The results show that the average weight of the three-year-old lenses (540.3 mg.) was 3.8 times heavier than that of the three- to four-week-old lenses (142.2 mg.). The percentage of water was less in the older lenses (60.3%) than in the younger lenses (70.1%). Although the lactic acid content of the older lenses was more than twice that of the young lenses (489γ compared with 227γ), the concentration per unit weight was less, 0.091% compared with 0.160%. Of particular interest is the observation that, while the older lenses contained 3.9 times as much protein as the younger lenses, there was no significant difference in the concentration of protein between the two lens groups (29.5% for older lenses and 28.9% for younger lenses).

The protein determinations were carried out on aliquots of the extract (young lens) and homogenate (old lens) prepared from a pool of 12 to 16 lenses. The values indicated represent averages per lens of the pool. The lactic acid determinations were performed on samples of various incubation mixtures at zero time. In separate determinations on the young lens extracts alone the average lactic acid content of 40 samples was 0.157% of the lens weights, average weight of lens being 138.0 mg. The H_2O content was determined on individual lenses whose average weight did not differ significantly from the indicated value.

Glucose as Substrate.—A. Young Lens (Table 2): In all experiments the lens ex-

TABLE 1.—*Analytical Data of Lens Groups*

	Wet Weight, Mg./Lens	H_2O, %	Lactic Acid		Protein	
			γ/Lens	%	Mg./Lens	%
A. Young Lens						
Av. of 17 samples	142.2	70.1	226.9	0.160	40.98	28.9
Standard deviation	18.5	1.1	36.4	0.026	5.1	1.7
Standard error	4.5	0.6	8.8	0.006	1.2	0.41
B. Old Lens						
Av. of 17 samples	540.3	60.3	489.0	0.091	159.0	29.5
Standard deviation	64.0	1.4	70.7	0.011	21.0	2.1
Standard error	15.6	0.29	17.2	0.003	5.1	0.5

TABLE 2.—*Lactic Acid Production from Glucose by Young Lenses* *

Expt. No.	Mg^{++} Molarity †	ATP, μM	AMP, μM	Lactic Acid μM		
				Per Lens	Per 100 Mg. Wet Weight	Per Mg. Protein
46-0	----	----	----	10.47	7.03	0.242
46-1	10^{-3}	----	----	10.94	7.36	0.253
46-2	10^{-2}	----	----	10.84	7.28	0.251
46-3	10^{-1}	----	----	1.28	0.86	0.030
46-4	10^{-3}	4.3	----	12.31	8.28	0.285
46-5	10^{-2}	----	8.7	16.06	10.79	0.372
46-6	----	4.3	----	11.42	7.68	0.264
47-7	----	----	8.7	13.36	8.97	0.309
50-0	10^{-3}	----	9.0	16.90	12.10	0.395
50-1	10^{-3}	4.5	9.0	17.80	12.80	0.416
50-2	10^{-3}	9.0	9.0	17.80	12.80	0.416
50-3	10^{-3}	18.0	9.0	11.70	8.40	0.273
50-4	10^{-3}	36.0	9.0	8.20	5.90	0.192
50-5	10^{-3}	9.0	18.0	8.90	6.40	0.208
50-6	10^{-1}	9.0	9.0	6.00	4.30	0.140
50-7	10^{-1}	18.0	9.0	7.80	5.60	0.182

* All values except Mg^{++} are in number of micromoles (μM) present in 1.8 ml. of incubation mixture. Time of incubation, 6 minutes at 37C; initial pH, 7.4. Gas mixture, 95% N_2 and 5% CO_2. Center well contained 1.0 ml. extract and 0.2 ml. hexokinase side-arms contained glucose (17.8μM; final concentration, 9.9×10^{-3} M); phosphate buffer, pH 7.4 (35.6μM; final concentration, 19.8×10^{-3} M), and the indicated materials at pH 7.4. Total volume, 1.8 ml. Experiment 46, lens weight 148.8 mg. and protein 29.0%; Experiment 50, lens weight 139.5 mg. and protein 30.7%. In absence of added glucose or hexokinase less than 2μM of lactic acid was formed per lens.

† Final molar concentration.

tract was fortified with 2 mg. hexokinase, 17.8μM glucose, and 35.6μM of phosphate buffer, pH 7.4. The results in Table 2 are given in terms of the micromoles of lactic acid produced in 60 minutes per lens, per 100 mg. wet weight of lens and per milligram of protein. Although it is clear that the addition of 10^{-2} M or 10^{-3} M Mg^{++} had only a slight (less than 5%) stimulating effect (Experiments 46-0, 46-1, and 46-2) in the absence of added nucleotides, 10^{-1} M (Experiment 46-3) exerted a marked inhibition. In the presence of added AMP (8.7μM-9.0μM) the production of lactic acid was increased considerably, the increase being greater in the presence of added Mg^{++} than in its absence (Experiments 46-5, 50-0, and 46-7). The addition of ATP (4.3μM-4.5μM) had only a slight activating effect, the increase being somewhat greater (14%, Experiment 46-4) in the presence of added Mg^{++} than in its absence (9%, Experiment 46-6). In the presence of added AMP (9.0μM) the addition of ATP (4.5μM-9.0μM) had no appreciable effect (Experiments 50-0, 50-1, and 50-2). Indeed, increasing concentrations of ATP resulted in marked reduction in the formation of lactic acid (Experiments 50-3 and 50-4). Comparison of Experiment 50-2 with Experiment 50-5 shows that 18μM of AMP caused a 50% reduction in lactic acid formation. In Experiment 46-3 a whitish precipitate was observed on mixing the Mg^{++} with the rest of the incubation mixture. That the observed inhibition may

TABLE 3.—*Lactic Acid Production from Glucose by Old Lenses* *

Expt. No.	Mg^{++} Molarity †	ATP, μM	AMP, μM	Lactic Acid, μM		
				Per Lens	Per 100 Mg. Wet Weight	Per Mg. Protein
47-0	----	----	----	12.7	2.53	0.089
47-1	----	----	8.97	22.8	4.54	0.161
47-2	----	----	17.94	26.7	5.32	0.188
47-3	10^{-3}	----	8.97	26.3	5.24	0.185
47-4	10^{-3}	----	17.94	28.9	5.76	0.204
47-5	10^{-3}	----	----	14.5	2.89	0.102
47-6	10^{-3}	4.1	----	14.8	2.95	0.104
51-0	10^{-3}	----	9.0	23.0	3.76	0.127
51-1	10^{-3}	----	18.0	26.1	4.26	0.144
51-2	10^{-3}	----	26.9	17.4	2.84	0.096
51-3	10^{-3}	4.5	9.0	22.2	3.63	0.123
51-4	10^{-3}	9.0	9.0	24.3	3.97	0.134
51-5	10^{-3}	18.0	9.0	24.8	4.05	0.137
51-6	10^{-3}	9.0	18.0	28.8	4.71	0.159

* Same description and conditions as in Table 2. Experiment 47, lens weight 502.0 mg. and protein 28.3%; Experiment 51, lens weight 611.9 mg. and protein 29.6%. In absence of added glucose or hexokinase less than 2μM of lactic acid was formed per lens.

† Final molar concentration.

have been caused by the reduction of the effective concentration of ATP and/or AMP from solution is suggested by the results of Experiments 50-6 and 50-7. Under the optimal conditions of the experiment 17.8μM lactic acid was formed per lens, representing a 50% conversion on the basis of the glucose added.

B. Old Lens (Table 3): In all experiments the lens homogenate was fortified with 2 mg. hexokinase, 17.8μM glucose, and 35.6μM phosphate buffer, pH 7.4. The results with two representative homogenates (Nos. 47 and 51) are given in Table 3 in terms of the micromoles of lactic acid produced in 60 minutes per lens, per 100 mg. wet weight of lens, and per milligram of protein. It is clear from the results that the addition of AMP caused a marked increase in the formation of lactic acid, an 80% increase by 9μM AMP and an 110% increase by 18μM AMP (Experiments 47-0, 47-1, and 47-2). Under these conditions, the addition of 10^{-2} M Mg^{++} had no appreciable effect (Experiments 47-3, 47-4, 51-0, and 51-1), although in the absence of added AMP, Mg^{++} had a small (14%) activating effect (Experiments 47-0 and 47-5). The presence of higher concentrations of AMP (26.9μM, Experiment 51-2) resulted in a 30% decrease in the production of lactic acid. The results also show that the addition of 4.5μM to 18.0μM ATP had no significant influence upon the production of lactic acid. Under the optimal conditions of the experiment about 81% of the added

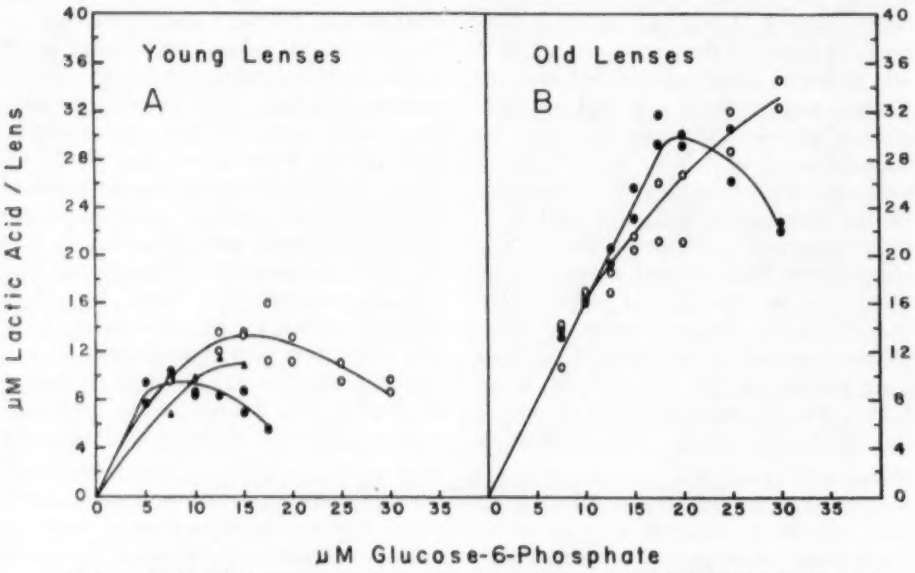

Fig. 1.—Effect of increasing concentrations of G-6-P upon lactic acid production per lens in the presence of varying concentrations of AMP. Values of subtrate are number of micromoles (μM) in 1.8 ml. of incubation mixture. *A*, young lenses; *B*, old lenses. Time of incubation, 60 minutes at 37 C; initial pH 7.4. Gas mixture, 95% N_2 and 5% CO_2. All flasks contained, in center well, 1.0 ml. of extract (young lenses) or homogenate (old lenses) and, in the side-arms, the substrate, Mg^{++} (final concentration, 5×10^{-3} M), phosphate buffer at pH 7.4 (twice the concentration of G-6-P), and the quantities indicated below of added AMP.

Symbols: open circles, results of two experiments with different lens preparations and with a ratio of G-6-P to AMP of 1:1; filled circles, results of two experiments with different lens preparations and with a ratio of G-6-P to AMP of 1:2; filled triangles, ratio of 1:0.5.

Lenses used, weight and protein content: In *A*: Open circles, 145.5 mg. and 26.9% protein; 121.7 mg. and 28.6% protein. Filled circles, 138.8 mg. and 30.8% protein; 145.5 mg. and 26.9% protein. Triangles, 180 mg. and 25.8% protein. In *B*: Open circles, 517.4 mg. and 29.6% protein; 510.6 mg. and 29.2% protein. Filled circles, 457.4 mg. and 27.3% protein; 479.7 mg. and 31.7% protein.

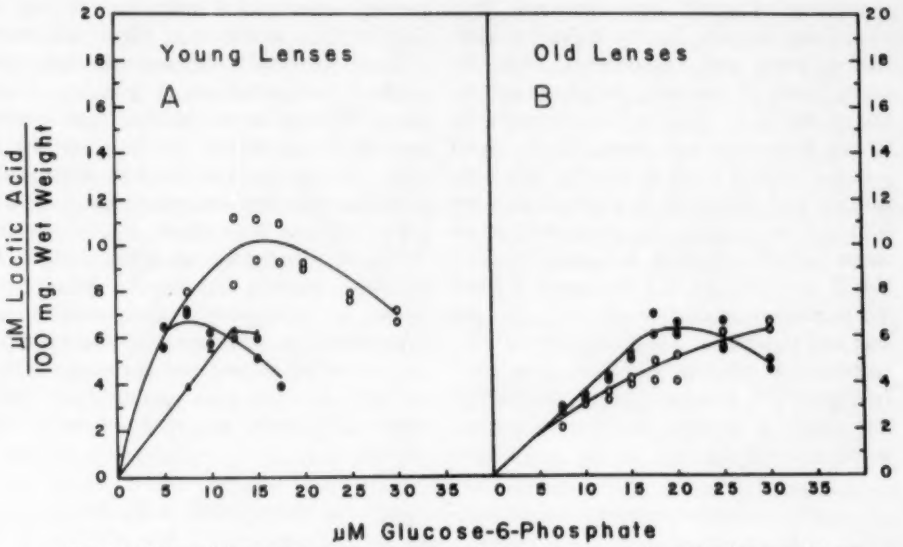

Fig. 2.—Effect of increasing concentrations of G-6-P upon lactic acid production per 100 mg. wet weight of lens in the presence of varying concentrations of AMP. Same description and conditions as in Figure 1.

glucose was converted to lactic acid (28.9µM).

Glucose-6-Phosphate as Substrate.—A. Young Lens: The results are graphically presented in Figures 1*A*, 2*A*, and 3*A* as plots of the number of micromoles of lactic acid produced per lens, per 100 mg. wet weight, and per milligram of protein, respectively, against increasing concentrations of substrate. The effects of different con-

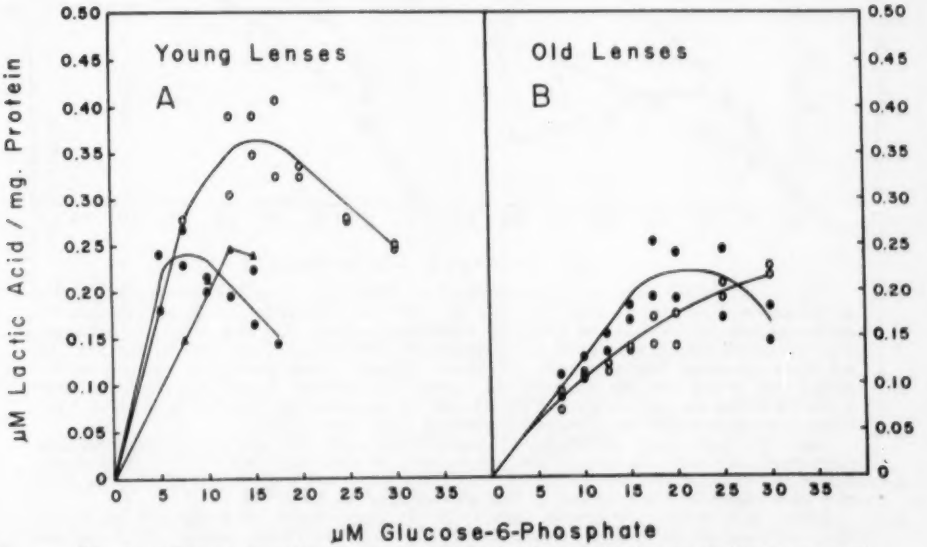

Fig. 3.—Effect of increasing concentrations of G-6-P upon lactic acid production per milligram of protein in the presence of varying concentrations of AMP. Same description and conditions as in Figure 1.

centrations of AMP were compared. It is clear from the data that the highest production of lactic acid was obtained when the molar ratio of substrate to phosphate acceptor was 1:1. The G-6-P concentration at this maximum was about 15μM. With a molar ratio of 1:0.5 about 16% less lactic acid per lens was formed, and the maximum occurred at a substrate concentration of about 15.0μM. Raising the molar ratio of G-6-P to AMP to 1:2 decreased further the maximum production of lactic acid per lens and resulted in a shift of optimal concentration of substrate to 7.5μM (Fig. 1*A*). In Figure 2*A*, however, the opposite effect was achieved, namely, the lactic acid produced per 100 mg. wet weight was higher with a ratio of 1:2 than with a ratio of 1:0.5, while, as shown in Figure 3*A*, there was no appreciable difference in lactic acid formed per milligram of protein. These small differences are, however, not considered to be significant. It is interesting to note that the slopes of the curves up to the maxima were the same when the ratio was either 1:1 or 1:2, while with a ratio of 1:0.5 the slope was somewhat smaller. In all three curves, moreover, a definite decrease in the amount of lactic acid formed was related to an increase of the substrate concentration beyond the optimum. (This is not too clear with the ratio of 1:0.5, since the curve was not extended far enough).

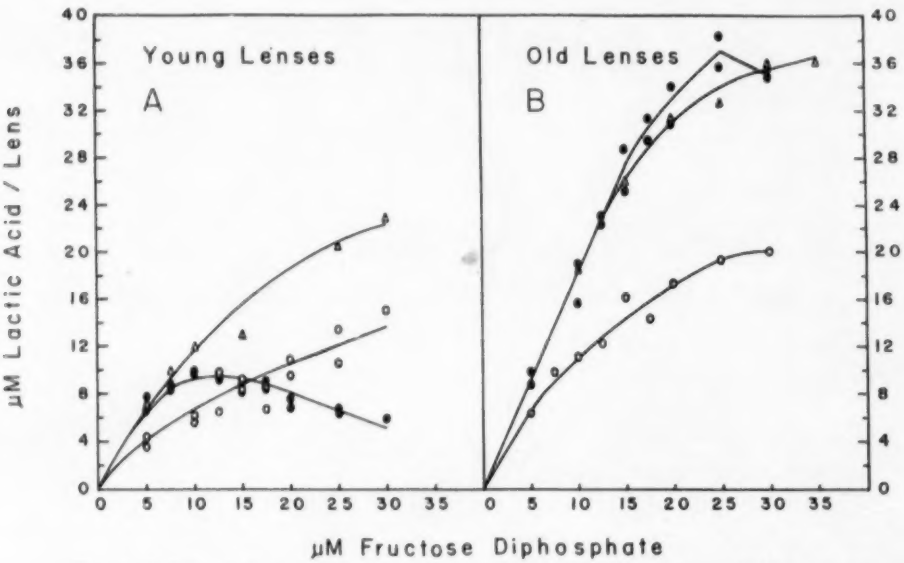

Fig. 4.—Effect of increasing concentrations of FDP upon lactic acid production per lens in the presence of varying concentrations of AMP and arsenate. Values of substrate are number of micromoles (μM) in 1.8 ml. of incubation mixture. *A*, young lenses; *B*, old lenses. Time of incubation, 60 minutes at 37 C; initial pH, 7.4. Gas mixture, 95% N_2 and 5% CO_2. All flasks contained, in center well, 1.0 ml. of extract (young lenses) or homogenate (old lenses) and, in side-arm, the substrate, Mg^{++} (final concentration, 5×10^{-3} M), phosphate buffer at pH 7.4 (twice the concentration of FDP), and the quantities indicated below of added AMP. When arsenate was present, phosphate buffer and AMP were absent.

Symbols: open circles, results of two experiments with different lens preparations (one experiment only with old lenses) and with a ratio of FDP to AMP of 1:1; filled circles, results of two experiments with different lens preparations and with a ratio of FDP to AMP of 1:2; triangles, arsenate present in final concentration of 5×10^{-3} M.

Lenses used, weight and protein content: In *A*: Open circles, 146.3 mg. and 28.7% protein; 139.3 and 26.7% protein. Filled circles, 125.4 mg. and 28.4% protein; 115.0 mg. and 27.8% protein. Triangles, 133.5 mg. and 30.2% protein. In *B*: Open circles, 518.6 mg. and 31.1% protein. Filled circles, 551.9 mg. and 33.0% protein; 609.7 mg. and 29.8% protein. Triangles, 552.7 mg. and 31.1% protein.

B. Old Lens: The results are graphically presented in Figures 1*B*, 2*B*, and 3*B*, next to those corresponding to the young lenses. It is apparent from an inspection of the curves that although with the 1:1 molar ratio of G-6-P to AMP the maximum production of lactic acid may not have been reached, continuation of the plots along the same trend would have resulted in only a slight increase in the amount produced. Indeed, for all practical purposes, it can be assumed, without affecting the significance of the results, that the maximum production of lactic acid with the 1:1 ratio was somewhat higher than with the 1:2 ratio, the difference being greater on a per lens basis than on a wet-weight or milligram-of-protein basis. To be sure, the difference did not exceed 20%. Of greater importance, however, was the observation that, because of the greater slope obtained with the 1:2 ratio at the maximum levels of lactic acid production, considerably more was formed per micromole of substrate present in the incubation mixture than with the 1:1 ratio. Indeed, for the indicated maxima, the excesses of the micromoles of lactic acid produced per micromole of substrate with the 1:2 ratio were, respectively, for Figures 1*B*, 2*B*, and 3*B*, 35%, 50%, and 42%.

The results also clearly show that with the 1:2 ratio increasing concentrations of substrate above the optimum resulted in a decrease in the production of lactic acid. Since with the 1:1 ratio the curves were not continued far enough, similar conclusions cannot be made in this case.

Fructose-1,6-Diphosphate as Substrate.—A. Young Lens: The results are graphically presented in Figures 4*A*, 5*A*, and 6*A* as plots of the number of micromoles of lactic acid produced per lens, per 100 mg. wet weight, and per milligram of protein, respectively, against increasing concentrations of substrate. The effects of different concentrations of AMP and of arsenate were compared. It is apparent from an inspection of the curves that although with the 1:1 molar ratio of FDP to AMP the maximum production of lactic may not have been reached, continuation of the plots along the same trend would have resulted in an insignificant increase in the amount produced. For all practical purposes, therefore,

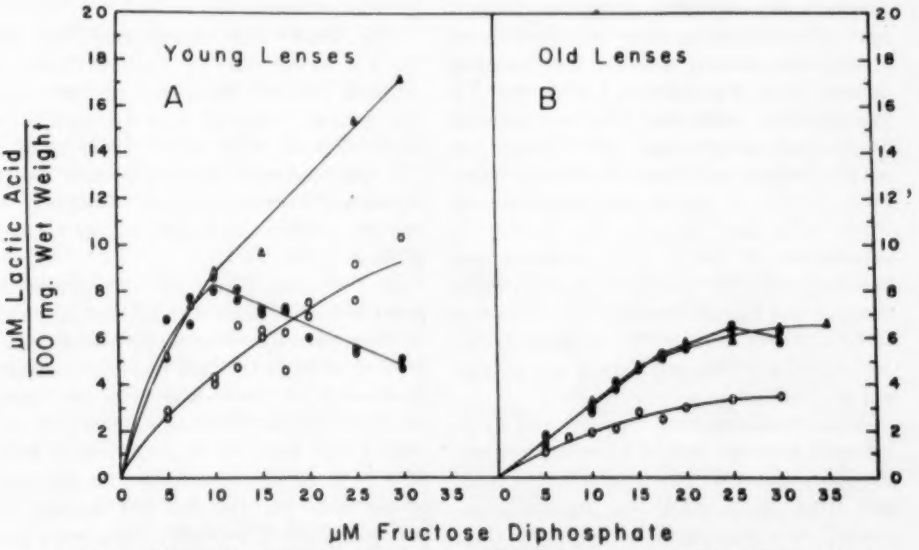

Fig. 5.—Effect of increasing concentrations of FDP upon lactic acid production per 100 mg. wet weight of lens in the presence of varying concentrations of AMP and arsenate. Same description and conditions as in Figure 4.

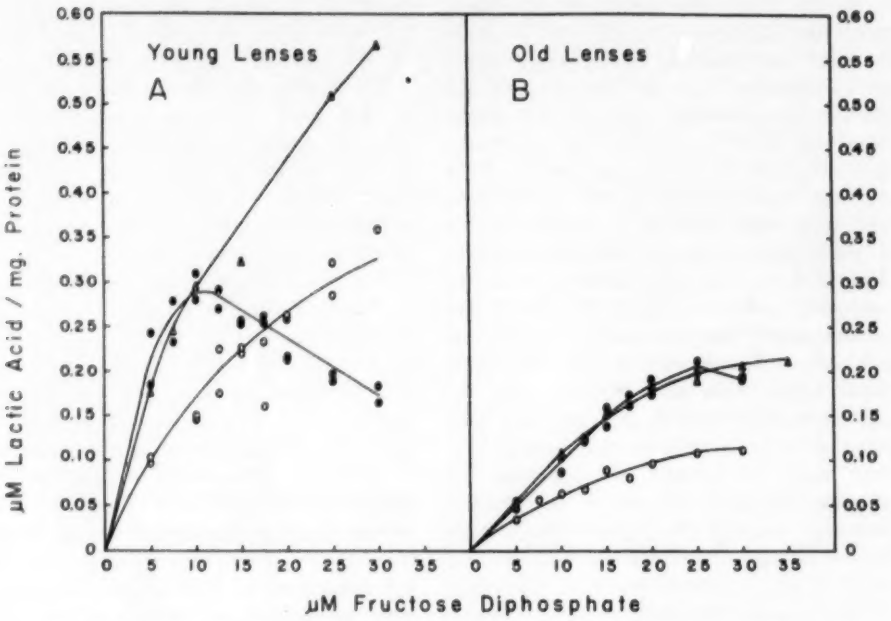

Fig. 6.—Effect of increasing concentrations of FDP upon lactic acid production per milligram of protein in the presence of varying concentrations of AMP and arsenate. Same description and conditions as in Figure 4.

it can be accepted that the indicated values represent the maximum production of lactic acid. On this basis, then, the quantity of lactic acid produced with the 1:1 ratio was greater than that produced with the 1:2 ratio by 45%, 12%, and 13%, respectively, on the basis of per lens, per 100 mg. wet weight, and per milligram of protein. However, because of the greater slopes of the curves with the 1:2 ratio, the number of micromoles of lactic acid produced per micromole of FDP present in the incubation mixture was higher than with the 1:1 ratio by 67%, 168%, and 140%, respectively, on the basis of per lens, per 100 mg. wet weight, and per milligram of protein.

When the incubation mixture was fortified with arsenate instead of with inorganic phosphate and AMP, the production of lactic acid from 30µM FDP was markedly increased over that produced with the ratio of FDP to AMP of 1:1 by 64%, 84%, and 73%, respectively, on the basis of per lens, per 100 mg. wet weight, and per milligram of protein.

The results also clearly show that with the 1:2 molar ratio of FDP to AMP increasing concentrations of substrate above the optimum resulted in a decrease in the production of lactic acid. Since with the 1:1 ratio and with arsenate present the experimental curves were not continued far enough, similar conclusions cannot be made in these cases.

B. Old Lens: The results are graphically presented in Figures 4*B*, 5*B*, and 6*B*, next to those corresponding to the young lenses. It is clear from the data that the maximum production of lactic acid with the molar ratio of FDP to AMP of 1:2 markedly exceeded that with the ratio of 1:1 by 85%, 83%, and 83%, respectively, on the basis of per lens, per 100 mg. wet weight, and per milligram of protein. Since with both ratios the maxima were reached with the same substrate concentration, i. e., 25µM

to 30μM of FDP, these values also express the relative activity of the systems.

No appreciable difference was noted between the results obtained with a molar ratio of FDP to AMP of 1:2 and when arsenate replaced AMP and inorganic phosphate.

The results also suggest that with the 1:2 molar ratio increasing concentrations of substrate above the optimum caused a decrease in the production of lactic acid. Since with the 1:1 ratio and with arsenate present the experimental curves were not continued far enough, similar conclusions cannot be made in these cases.

Comment

In an intact tissue such factors as the spatial location of the enzymes, pH or thermodynamic considerations, low apoenzyme concentration, coenzyme or activator deficiency, permeability, and the presence of natural inhibitors serve to control the functional metabolic activity of the system. In cell-free extracts or homogenates, however, fortified with additions of the various necessary coenzymes and activators and maintained at a given pH, the most important factors become the relative content or concentration of the individual enzymes in a multienzyme system and the nature of the enzymes.

With regard to the latter consideration, the results of this investigation suggest that the experimental lens preparations of the two age groups follow, in general, similar metabolic patterns in their behavior with the tested substrates. Thus, both lens preparations, in the presence of glucose as a substrate, manifest a relative deficiency of hexokinase and adenosinetriphosphatase and depend upon an exogenous source of phosphate acceptor for the maintenance of an active glucolyzing system. Furthermore, they both display the ability of producing maximum amounts of lactic acid in the presence of an optimum concentration of AMP and an excess of AMP results in an inhibition of the metabolic activity. In addition, in both lens preparations sufficient ATP is present at least to initiate the reaction, since no absolute requirement for the addition of this energy-rich compound could be demonstrated. The same was true with Mg^{++}.

Similarly with G-6-PO_4 and FDP as substrates, the optimal production of lactic acid depended upon a favorable ratio of substrate of AMP, and when the concentration of AMP was increased the production of lactic acid tended to decrease. As for the experiments with FDP in which arsenate replaced AMP and inorganic phosphate, the difference in behavior can be adequately explained on a comparative quantitative basis rather than as a reflection of a qualitative enzymatic difference (see below). On the basis of the present studies, therefore, it seems safe to conclude that the qualitative properties of the lens enzymes associated with the Embden-Meyerhof scheme were not apparently affected and that there is no shift in the major metabolic pathway of the normal lens between the ages of 3 weeks and 3 years.

In view of the foregoing discussion, it is reasonable to state that a comparative evaluation of the ability of the two lens preparations to produce lactic acid under the optimal conditions of the experiments is a reflection of the relative content or concentration of the enzymatic apparatus in the tissues. This property may be properly referred to as the functional capacity of the particular lens preparation.

TABLE 4.—*Comparison of Lactic Acid Production by Young and Old Lenses Under Optimal Conditions*

Substrate	μM Lactic Acid by Young Lenses / μM Lactic Acid by Old Lenses		
	Per Lens	Per 100 Mg. Wet Weight	Per Mg. Protein
Glucose	0.62	2.22	2.04
G-6-P	0.40	1.62	1.65
FDP	0.37	1.44	1.58
FDP+AsO_4	0.61	2.65	2.63

$\frac{\text{Wt. of Old lens}}{\text{Wt. of young lens}} = 3.8$

Protein
Young lens, 28.9%
Old lens, 29.5%

A summary of the metabolic activities of the two lens groups is presented in Table 4. Considering the whole lens as the unit of growth and development, it is apparent that with age there is a marked increase in the capacity to produce lactic acid. The reciprocals of the values in the second column show that the increase with glucose, G-6-PO_4, and FDP as the substrates were 61%, 150%, and 170% with AMP and 64% with arsenate, respectively. The wide range of values is not so much a reflection of great differences between the capacities of the two lens groups for the indicated substrate as it is expressive of relatively small differences in the quantities of lactic acid produced from the various substrates for each lens group. Thus, for the young lenses, except for FDP with arsenate, the maximum amount of lactic acid produced was 17.8μM with glucose, 13.8μM with G-6-P, and 13.5μM with FDP in the presence of AMP. Only when the arsenate was present did a marked increase (from 13.5μM to about 23μM) in lactic acid production occur. With the old lenses the values were more constant, 28.8μM with glucose, 34.5μM with G-6-PO_4, 37μM with FDP and AMP, and 35.5μM with FDP and arsenate. With regard to the action of arsenate, it is well known [17] that in anaerobic carbohydrate metabolism arsenate causes an uncoupling of the phosphate acceptor system from the production of lactic acid. The observed acceleration in the production of lactic acid indicates that, in the experiments with FDP using young lens extracts, the reactions mediated by the enzymes 3-phosphoglycerate kinase and pyruvate kinase† are rate-limiting and tend to limit the rate of formation of lactic acid. This is probably due to the limited concentrations of one or both of the indicated enzymes. The absence of any stimulatory effect of arsenate upon the rate of formation of lactic acid from FDP with the old lens preparations clearly indicates that the transphosphorylating enzymes are present in this system in concentrations sufficient to give reaction rates similar to those corresponding to the nonenzymatic spontaneous reactions occurring in the presence of arsenate.‡ On the basis of the production of lactic acid, therefore, the results support the view that the increased functional capacity of the older lenses compared with the younger lenses is largely due to the relatively greater content of active enzymes on a whole-lens basis. It is to be noted, moreover, that the higher optimal concentration of AMP relative to that of the substrate (at least for glucose and FDP) required by the old lenses also reflects the relatively greater content of transphosphorylating enzymes present.

Rather good agreement exists amongst investigators that with advancing age there is a decrease in over-all metabolic activity when the latter is based upon wet weight or protein content of the tissue. The data in the last two columns of Table 4 also show that the capacity of the old lenses to produce lactic acid when this is calculated on the basis of 100 mg. wet weight or milligram of protein content is considerably smaller than that of the young lenses.

The correlations inherent in the data of Table 4 are indeed of great interest. When viewed from the perspective of an intact whole tissue, the results clearly indicate that with age the capacity of the lens to derive energy from glucose under anaerobic conditions is distinctly increased. However, while the increase in metabolic activity is between 60% and 170%, the increase in weight of the lens is 280%, indicating that

† 3-Phosphoglycerate kinase mediates the following reaction:

$$\left(\begin{matrix}\text{3-phosphoglyceryl phosphate}+\text{ADP}\\ \text{(AMP)}\end{matrix}\right)=\left(\begin{matrix}\text{3-phosphoglyceric acid}+\text{ATP}\\ \text{(ADP)}\end{matrix}\right)$$

Pyruvate kinase mediates the following reaction:

$$\left(\begin{matrix}\text{phosphopyruvate}+\text{ADP}\\ \text{(AMP)}\end{matrix}\right)=\left(\begin{matrix}\text{pyruvate}+\text{ATP}\\ \text{(ADP)}\end{matrix}\right)$$

‡ In the presence of arsenate 3-phosphoglyceryl arsenate instead of the 3-phosphoglyceryl phosphate is formed and this undergoes spontaneous hydrolysis to form 3-phosphoglycerate. Similarly, phosphopyruvate is presumed to split spontaneously to pyruvate and inorganic phosphate.

the metabolic activity of the lens did not keep pace with the increase in weight. The data in the column under 100 mg. wet weight substantiate this phenomenon for each substrate and for the particular lenses used. Of further significance is the observation that although the protein concentration of the lens did not change with age (28.9% for the young and 29.5% for the old lenses), the metabolic activity per milligram of protein decreased from 60% to 100% when AMP was added and 163% when arsenate was present. Thus, despite an increase in over-all metabolic activity accompanying growth and development of the lens, the functional metabolic efficiency per unit weight or per unit protein steadily decreased. This may be related to the decreased concentration of soluble proteins and proportional increase in concentration of insoluble albuminoids, changes which are characteristic of the aging processes in lens.[18]

Our present knowledge of the anatomical and histological changes associated with advancing age of the lens, both animal and human, are compatible with the above-described biochemical observations. During the life of the normal lens, fibers are continually being formed in the region of the equator. As new fibers are laid down the older fibers are compressed and pushed in toward the center, where they gradually lose their nuclei and become dense and yellowish. They increase in refractive index and decrease in width and thickness, and they constitute the nuclear region of the lens. In a younger lens there is a relatively greater abundance of proliferating epithelium cells at the equator and consequently a greater number of younger fibers. Unlike other tissues of ectodermal origin, like the skin, nails, and hair, where the exfoliation of the oldest cells serves to maintain a state of dynamic equilibrium with the newer cells, no such shedding is possible in the lens, which is completely shut off from the outside environment. In this case compensation takes place by a diminution in volume of the oldest fibers through a process of shrinking and formation of a dense nucleus. This diminution in volume attended by a slight loss of water content of the fibers does not fully offset the appositional growth, and so the lens keeps on enlarging even in advanced life. When the process of growth has proceeded to the point where the sclerosis of the nucleus results in impairment of light transmission, then visual acuity suffers and the condition is pathologic. True, senile cataracts, on the other hand, concern loss of transparency of the cortical area outside of the nucleus and always represent a pathologic condition. They do not represent an aging process, since many people live a long life with entirely transparent lenses. What causes the normal aging pattern of metabolic activity to become deranged and result in pathologic deviation can not be answered at present. Not only must considerably more experimental work be done on young and old lenses but, of greater importance, is the need for comparative studies with lenses in different old-age groups.

Summary

The ability of extracts of lenses from 1-month-old rabbits to produce lactic acid under anaerobic conditions from glucose, glucose-6-phosphate, and fructose diphosphate has been compared with that of lenses from 3-year-old rabbits.

The older lenses weighed on the average 540 mg. and contained 60% H_2O and 29.5% protein; the corresponding values for the younger lenses were 142 mg., 70%, and 28.9%.

Both lens preparations displayed relative deficiences of hexokinase and adenosinetriphosphatase. Consequently, with glucose as a substrate, hexokinase, inorganic phosphate, and adenosine-5-phosphate were added to the extracts, while with glucose-6-phosphate and fructose diphosphate only inorganic phosphate and the nucleotide were added. In all cases the maximum, or optimal, quantity of lactic acid produced was dependent upon an optimal concentration ratio of sub-

strate to phosphate acceptor. In general, in the two age groups the qualitative properties of the lens enzymes associated with the Embden-Meyerhof scheme were not apparently different and there was no shift in the major metabolic pathway of the normal lens between the ages of 3 to 4 weeks and 3 years.

On the basis of the whole lens as a unit of growth and development, the capacity of the older lenses to produce lactic acid from the substrates tested exceeded that of the younger lenses by 60% to 170%. However, when this capacity was calculated on the basis of activity per 100 mg. wet weight or per milligram of protein, the younger lenses showed the greater metabolic efficiency.

The observed biochemical changes are compatible with our understanding of the anatomical and histological changes associated with advancing age of the normal, transparent lens.

Dr. Irving H. Leopold, Director of Research, gave encouragement during the course of this investigation.

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Visual Field Defects Due to Optic Nerve Compression by Mass Lesions

MAX CHAMLIN, M.D., New York

In 1893, Gowers [1] gave unilateral loss of sight and of smell as a lateralizing sign of frontal tumor. In 1905, Schultz-Zehden [2] published a clinical and postmortem report of a frontal tumor with profound optic atrophy in one eye and severe papilledema in the other. He stated, "We have before us in the foregoing case, a double action by the tumor. In the one eye it led to atrophy by direct compression of the optic nerve; in the other it acted directly to destroy it by raising the intracranial pressure." In 1906, Wilbrand and Saenger [3] reported a similar case and explained that the absence of papilledema in the atrophic nerve head was due to the shutting off by the tumor of the meningeal spaces, thus preventing the cerebrospinal fluid from circulating into the optic nerve sheath on that side.

In 1909, Leslie Paton [4] wrote his famous paper in which he reviewed 200 brain tumors ophthalmoscopically examined by Marcus Gunn or himself. In it, he spoke of those patients in whom unilateral loss of vision had occurred and said, "These cases show that direct pressure on the optic nerve or the chiasma may cause loss of vision and pressure atrophy without causing optic neuritis." He used the term "optic neuritis," but he was actually referring to papilledema, because, at that time, the inflammatory theory of papilledema was still widely accepted despite Horsley's contention that it was mechanical. However, two years later, in 1911, Paton and Holmes [5] substantiated Horsley's contention and established optic neuritis and papilledema as separate entities.

Received for publication Jan. 2, 1957.

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The same year, 1911, Foster Kennedy [6] wrote his famous paper describing in great detail the effect of frontal tumors on optic nerves more fully than had been done before, though one or more of his observations and deductions were already well known to each of the men mentioned before, namely, Gowers, Schultz-Zehden, Wilbrand and Saenger, and, certainly, Paton.

Geoffrey Jefferson,[7] in his Doyne Lecture delivered before the Oxford Ophthalmological Congress in 1945 (and from which I have borrowed immodestly for this short history), observes, "We shall not begrudge Foster Kennedy his own important contribution, and although, after the evidence adduced here it may seem to be a "non sequitur" to continue the attachment of his name to the syndrome, it seems to be useless at this day to amend it, so world-wide has the acceptance been."

It is from this background that the famous Foster-Kennedy syndrome has come down to us. This syndrome stated that a frontal tumor caused "true retrobulbar neuritis with the formation of a central scotoma and primary optic atrophy on the side of the lesion, together with concomitant papilledema in the other eye."

It seems regrettable that he should have used the term "retrobulbar neuritis," rather than limiting himself to actual observation of the so-called "central scotoma."

Jefferson,[8] in commenting on this point said, "To begin with, we should abandon any further mention of 'retrobulbar neuritis,' —a difficult enough pathological concept without invoking it unnecessarily. Clearly, the cause of the scotoma and of the atrophy is plain compression. . . ."

The marked emphasis on the central scotoma being due to compression of the optic nerve has made a rather firm impression on our modern concept in neuro-ophthalmology, although its incidence in relation to other types of field defects caused by mass compression has not been clearly established. This incidence is especially important since a true central or cecocentral scotoma is very characteristic of toxic or inflammatory conditions and may therefore cause confusion in the differential diagnosis between a defect due to mass compression and one due to inflammatory lesion of the optic nerve.

Old concepts are sometimes handed down and continue to be accepted without sufficient critical analysis. Therefore, when I reviewed all my cases of optic nerve compression by mass lesions and became aware of the scarcity of true "central" scotomas, I decided to review the recent literature on this subject and compare it with my own experiences.

In reviewing the recent literature on this subject, it was apparent that the term "central" scotoma due to optic nerve compression by mass lesions was being used somewhat loosely in some of the cases. Specifically, it was being used in three categories of cases which did not serve to explain the total effect of mass compression on the optic nerve. For the sake of simplicity let us call these categories by the following names: (1) blind spot enlargement, (2) use of inadequate visual stimuli, and (3) chiasmal interference.

1. Blind spot enlargement: In some cases of optic nerve compression with papilledema there was rather marked blind spot enlargement, the pericecal defect encroaching on the fixation area and causing a diminution in central vision. Surely, this is not a central scotoma due to optic nerve compression affecting the supposedly more vulnerable central macular fibers.

2. Use of inadequate visual angle: In some cases the term "central scotoma" was applied to a central defect with a poorly defined edge to the scotoma, and the peripheral fields in the same case were examined with visual angles much larger than those used to detect the central scotoma. This inadequacy of size of the visual angle used produced a field showing what was reported as a central scotoma with an intact periphery. Actually, if the proper small visual angle had been used for examination of the peripheral field in these cases breaking-through of the scotoma to the periphery might well have been shown in some of the cases.

3. Chiasmal interference: In cases of chiasmal interference, the inner isopters are known to be affected before the periphery. Thus, it is well known that the field for 1/2000 white shows upper temporal hemianopic defects in the 10 to 20 degrees of arc area, or "intermediate field," before central involvement is evident. This is well illustrated in Traquair's [9] description of both "nonscotomatous" and "scotomatous" field defects due to chiasmal interference. In 1950, Chamlin and Davidoff [10] offered a theoretical explanation of the vertical arrangement of the fibers in the chiasma to account for the early involvement of the intermediate field. Essentially, it postulated a mechanical etiology due to proximity of the tumor to the fibers representing the intermediate field. In any event, the well-known separation of nasal from temporal bundles and the resultant constant hemianopic defects offer an excellent clinical basis for diagnosis of a mass lesion at the chiasm and therefore furnish an excellent basis for differentiating it from loss of vision due to inflammatory disease such as retrobulbar neuritis. Therefore, the central involvement in chiasmal interference is due to contiguity of involvement from the defective "intermediate" field, and it is not a true "central" scotoma. On the same subject, Walsh [11] is also of the opinion that a true central scotoma does not occur in chiasmal interference, and he states that he has seen only one case of unilateral central scotoma with chiasmal interference. He says that the testing was incomplete in this case and that there was evidence of peripheral defect as well.

Taking care to eliminate those cases falling within the three categories mentioned above, I reviewed the recent English literature on the effect of mass compression of the optic nerve. Traquair,[12] in discussing the effect of pressure on the optic nerve, states that "the field changes are, as a rule, wide sector depressions of irregular quadrantic or hemianopic shape producing different forms of vertical or horizontal hemianopia, or defects which tend in that direction." He demonstrates three fields showing the effect of pressure on the optic nerve. Only in Case B does a small central scotoma seem to be present, although he mentions that the pericecal defect may well be due to blind spot enlargement. In Cases A and C break-through to the periphery is seen.

Jefferson,[7] in his Doyne Lecture, discussed five cases of mass compression, in four of which visual fields could be plotted. Cases 1, 2, and 4 showed typical chiasmal interference. In Case 3, while a central scotoma was shown for 5/2000 white, the periphery was tested only with 10/330 white, a visual angle 12 times as large as the one used to detect the central defect. It may well be, therefore, that if an appropriately small visual angle had been used for the peripheral field break-through might have been demonstrated, probably to the upper nasal end of the scotoma shown.

In 1944, Schlezinger, Alpers, and Weiss [13] wrote on the scotomatous field defects due to suprasellar meningiomas. They describe four cases and show a central scotoma in several of the fields. Thus, in case 1 the left eye shows a central scotoma. However, the periphery also shows definite contracture with 3/330 white, and it is possible that break-through might have been demonstrated with 1/330 white. In Case 2 the right eye also shows a central scotoma but peripheral defect is present as well, even though a 10/330 test was used. Break-through would be likely here with a smaller visual angle. Cases 2 and 4 showed break-through. The authors state, "In addition to the outline of the central defect, which at times may be fully developed when the patient is first seen, an important characteristic of such fields is the peripheral indentation which is almost always present and which sooner or later merges with the central defect to produce an expanding sector defect in the visual field."

In 1949, Mooney and McConnell [14] reported seven cases of mass compression of the optic nerve. Five of their cases fell into the three categories mentioned earlier in this paper. Their Cases 3 and 4 showed definite central scotomas. They give strong evidence to support the view that pressure on the intracranial portion of the ophthalmic artery is a factor in the production of scotomata.

Again in 1949, Meadows [15] reported 11 cases of optic nerve compression by mass lesions. In one case (Case II) he shows a rather well-defined central scotoma. In the other cases where fields were demonstrated, peripheral break-through or indentation is very evident, while in still other cases chiasmal involvement is evident. He concludes that early peripheral loss may pass unnoticed and that only the central involvement may be noted. He goes on to say that the field defect in early cases "may consist of a central scotoma, but by the time the patient first consults his medical advisor there is often a gross central scotomatous defect breaking through to the periphery at one point."

Thus, of the 28 cases by Traquair, Jefferson, Schlezinger et al., Mooney and McConnell, and Meadows, only 4 cases seemed to present convincing evidence of a true central defect with an intact periphery. One might suggest that even in these cases, where peripheral field testing was done with 1/330, minimal techniques such as "rapid comparisons" [16] and "simultaneous stimulation" [17] might very well have brought out some peripheral involvement.

Present Cases

I found the following types of cases most suitable for this study: sphenoid ridge meningioma, olfactory groove meningioma, orbital tumor, and frontal meningioma.

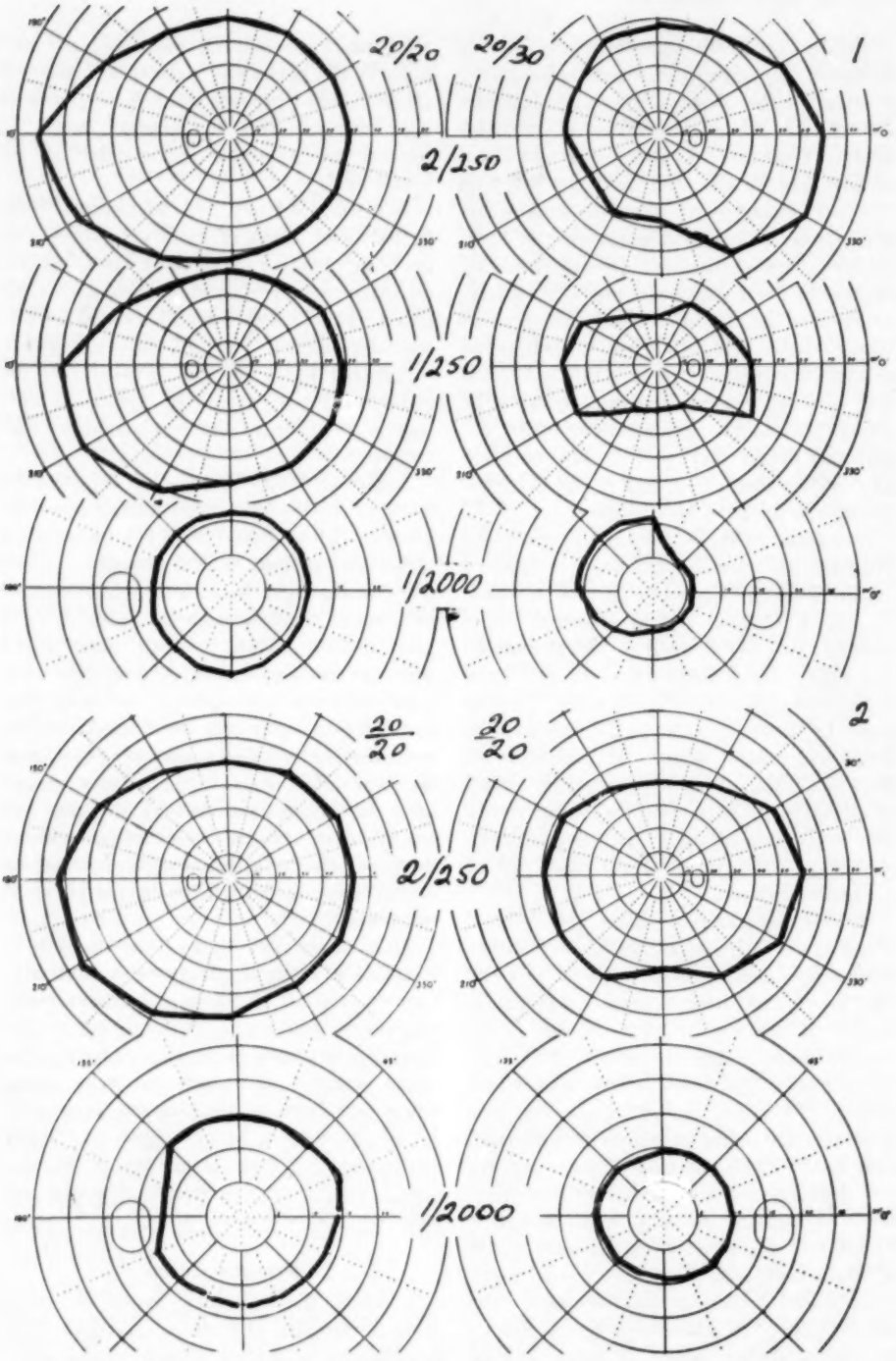


Fig. 1 (Cases 1 to 9).—Nine cases of sphenoid ridge meningioma with visual field defect in one eye only.

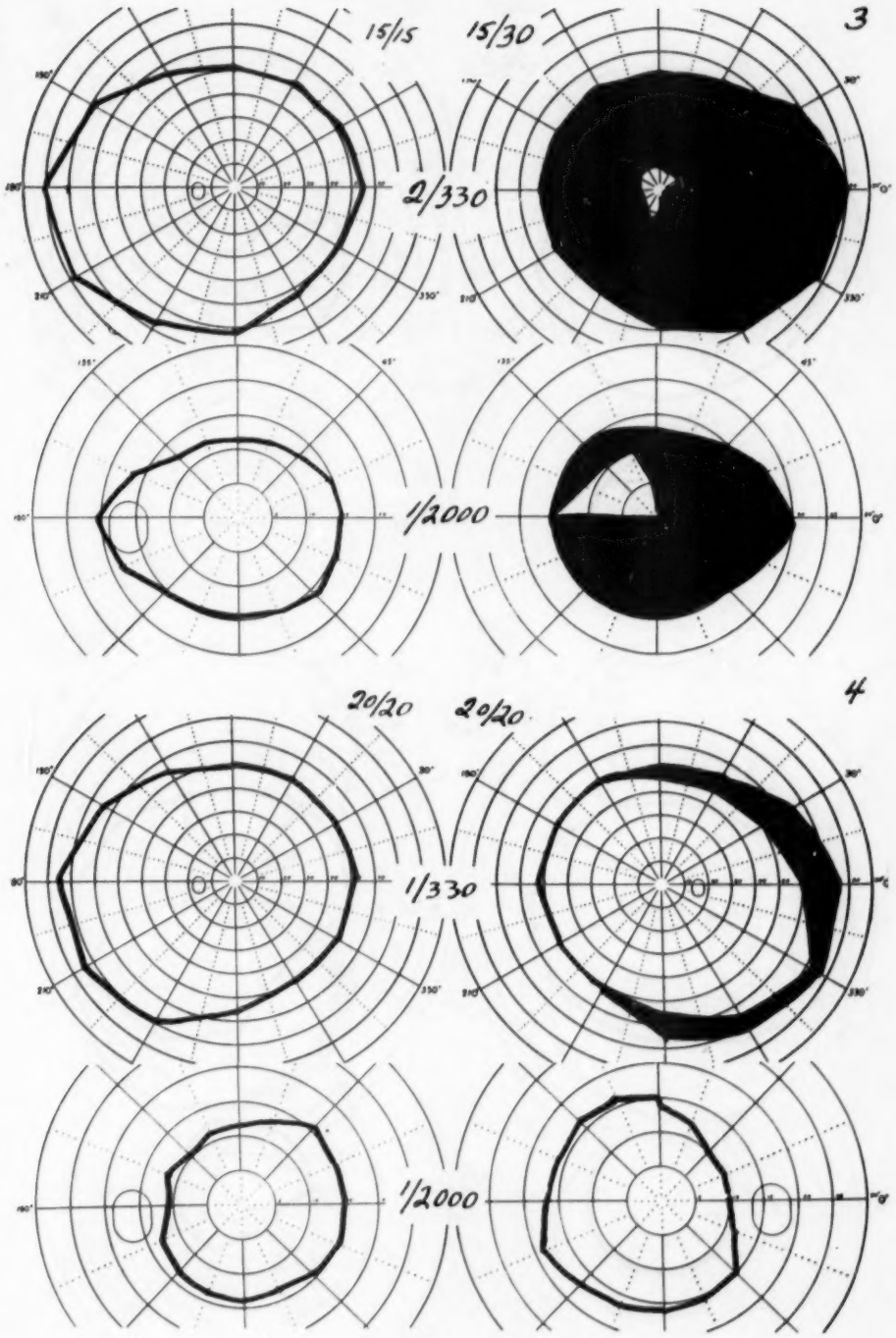
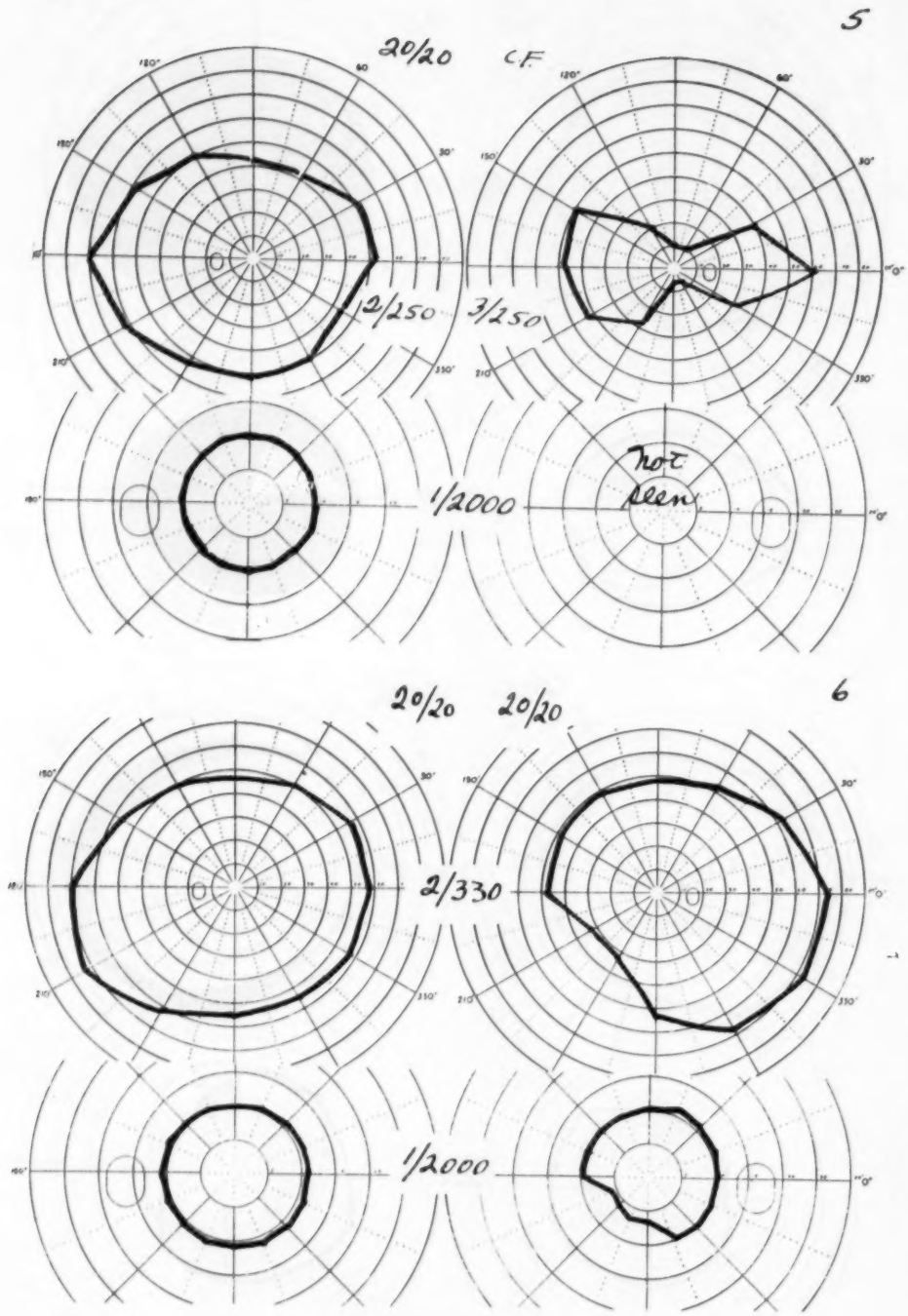


Fig. 1 (*Continued*)



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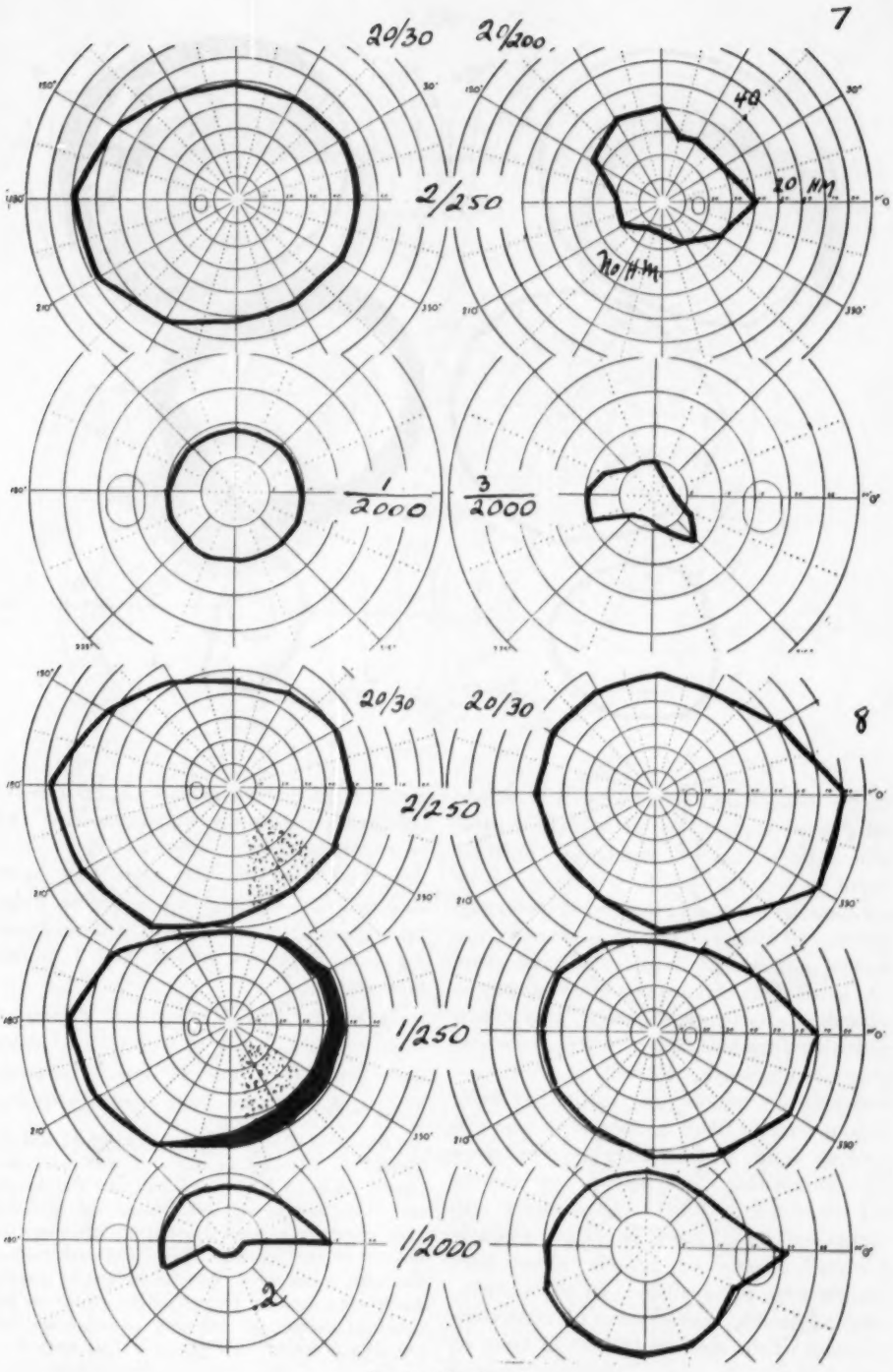

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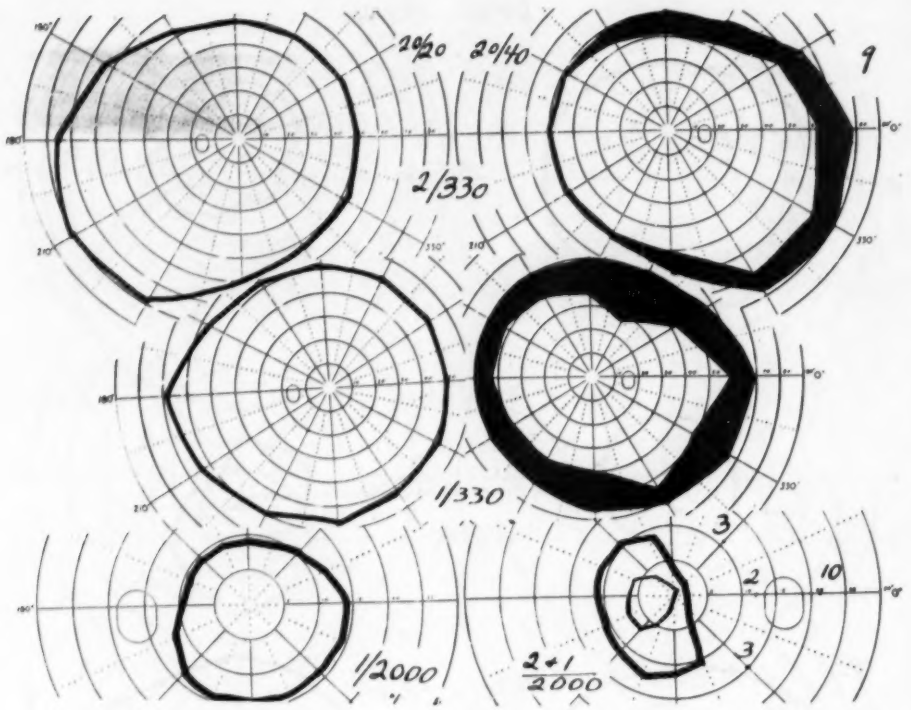

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All those cases which were not verified surgically or by other completely reliable diagnostic tests were eliminated. Furthermore, in keeping with the criteria set up by eliminating the three categories mentioned before, all cases in which the tumors extended posteriorly to involve the chiasm were not used. This eliminated a good number of olfactory groove meningiomas, tuberculum sellae meningiomas, and even some sphenoid ridge meningiomas, as well as aneurysms and pituitary tumors. In addition, all those lesions which caused amaurosis of one eye without in any way affecting the other were also eliminated, since neither eye showed the sequence of field involvement. I also eliminated those cases in which adequate hospital records or reliable visual field studies were not available. In other words, only adequately studied cases of mass compression of the optic nerve well in front of the chiasm were used. Therefore, from a rather large number of cases of optic nerve compression, seen by me in the last few years, those suitable for this report were narrowed down to 24, and these were classified as follows: 14 sphenoid ridge meningiomas, 5 olfactory groove meningiomas, 3 orbital tumors, and 1 frontal lobe tumor.

Sphenoid Ridge Meningiomas (Fourteen Cases).—In Cases 1 to 9 the visual fields were involved in one eye only.* In Cases 1, 2, 3, 4, 5, 6, and 7 the central field was

* Note that in some cases defective field was indicated by blacking in the area with ink completely, while in other cases the area was simply left blank and in still other areas the defective area merely had some denotations indicating the quality of the defective field. The last method has been found most desirable in that it gives a much more accurate picture of the quality of the field and enables the examiner to judge whether the edge is "steep" or "sloping." This method of qualifying defective field was described in 1952.[10]

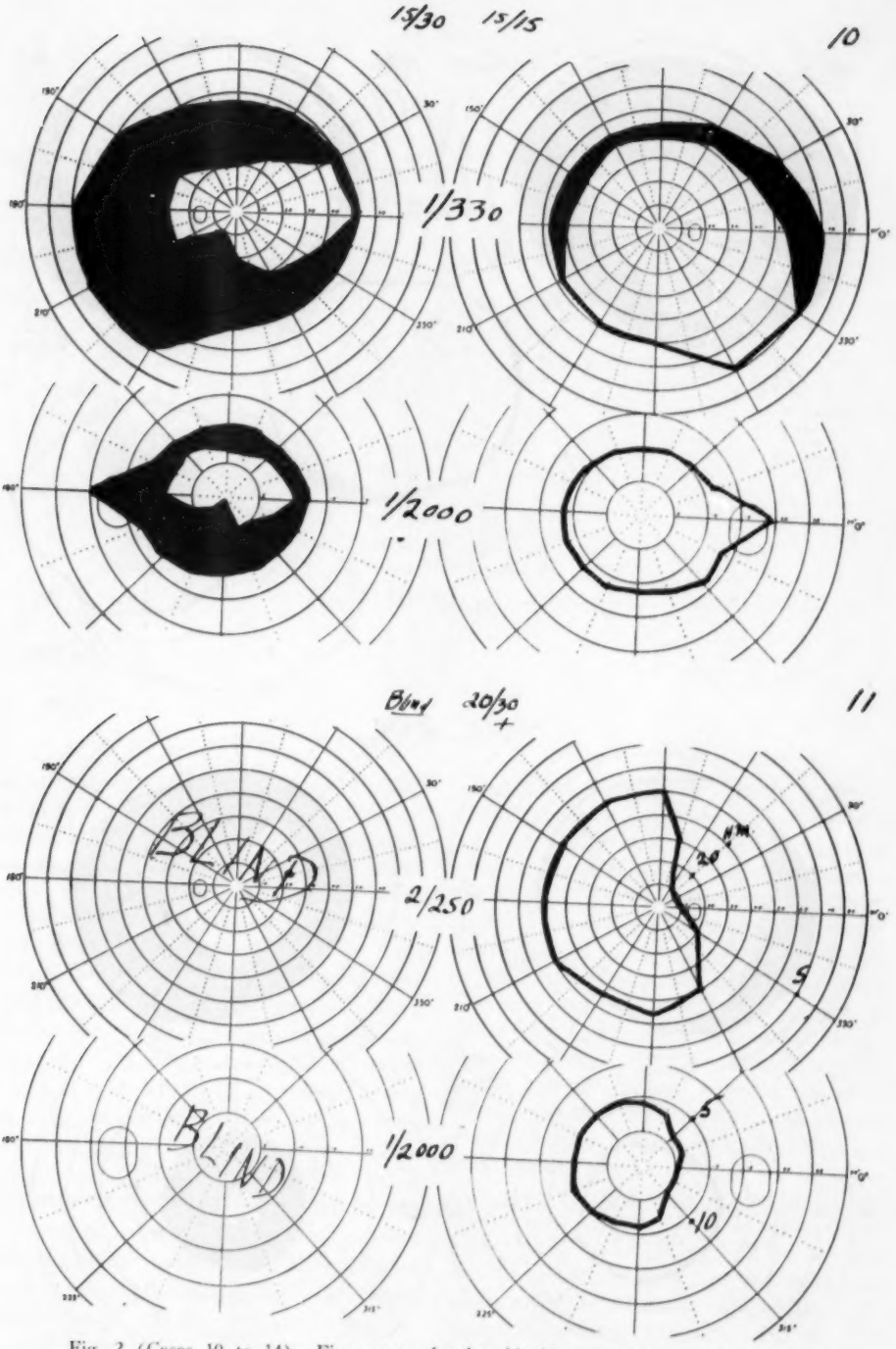
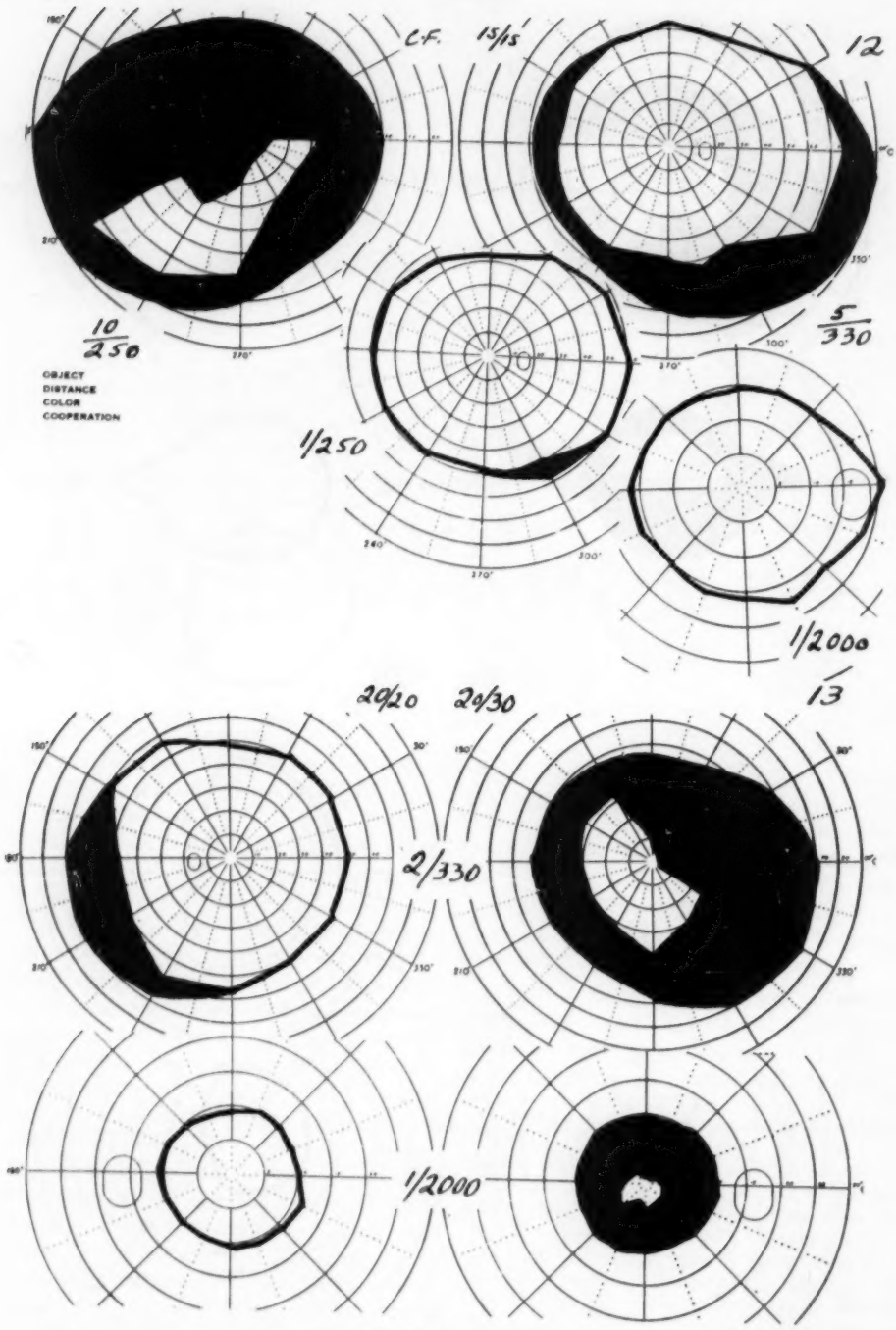


Fig. 2 (Cases 10 to 14).—Five cases of sphenoid ridge meningioma with bilateral involvement of visual fields.



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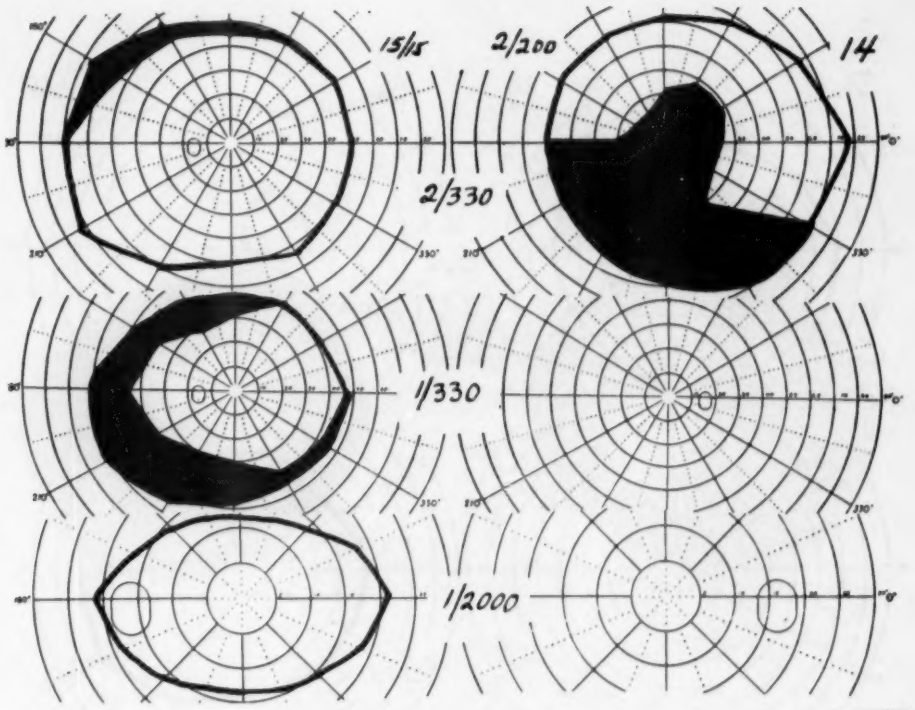


Fig. 2 (*Continued*)

encroached upon but so was the corresponding peripheral field. It may be said that the amount of peripheral and central field involvement was "proportionate" in these cases. In Cases 8 and 9 the central isopters seemed to show relatively greater involvement than the peripheral isopters. In Case 8, while there was a pronounced lower defect for 1/2000 white, on the other hand, when "qualifying" [19] the defective area, it was found that a 2 mm. test object was seen as far down as 10 degrees below, indicating that the defect was not very dense. Furthermore, beside the slight lower nasal peripheral contracture for 1/250 white in the left eye, it was found that the whole lower nasal periphery was poor when compared with other portions of the peripheral field equidistant from fixation. This was done by "rapid comparisons," and the area involved is indicated by stippling.

In Case 9 the right eye showed a rather marked contracture of the inner isopters, i. e., for 1/2000 and 2/2000, as compared with the peripheral contractures. However, this patient had frank papilledema of the right eye, and a good deal of the temporal contracture of the inner isopters may well be due to the enlargement of the blind spot. This case, then, falls into the category of "blind spot enlargement" mentioned above. However, the benefit of the doubt was given to this case as showing a contracted inner isopter, and thus we have two cases (Cases 8 and 9) where the inner isopter contractures predominated.

In the other five cases (Cases 10 to 14) there was bilateral involvement of the visual fields. In Cases 10, 11, and 12 the left eye was involved primarily and the right eye secondarily. In Cases 13 and 14 the right eye was involved primarily and the left secondarily. In all five cases the contralateral

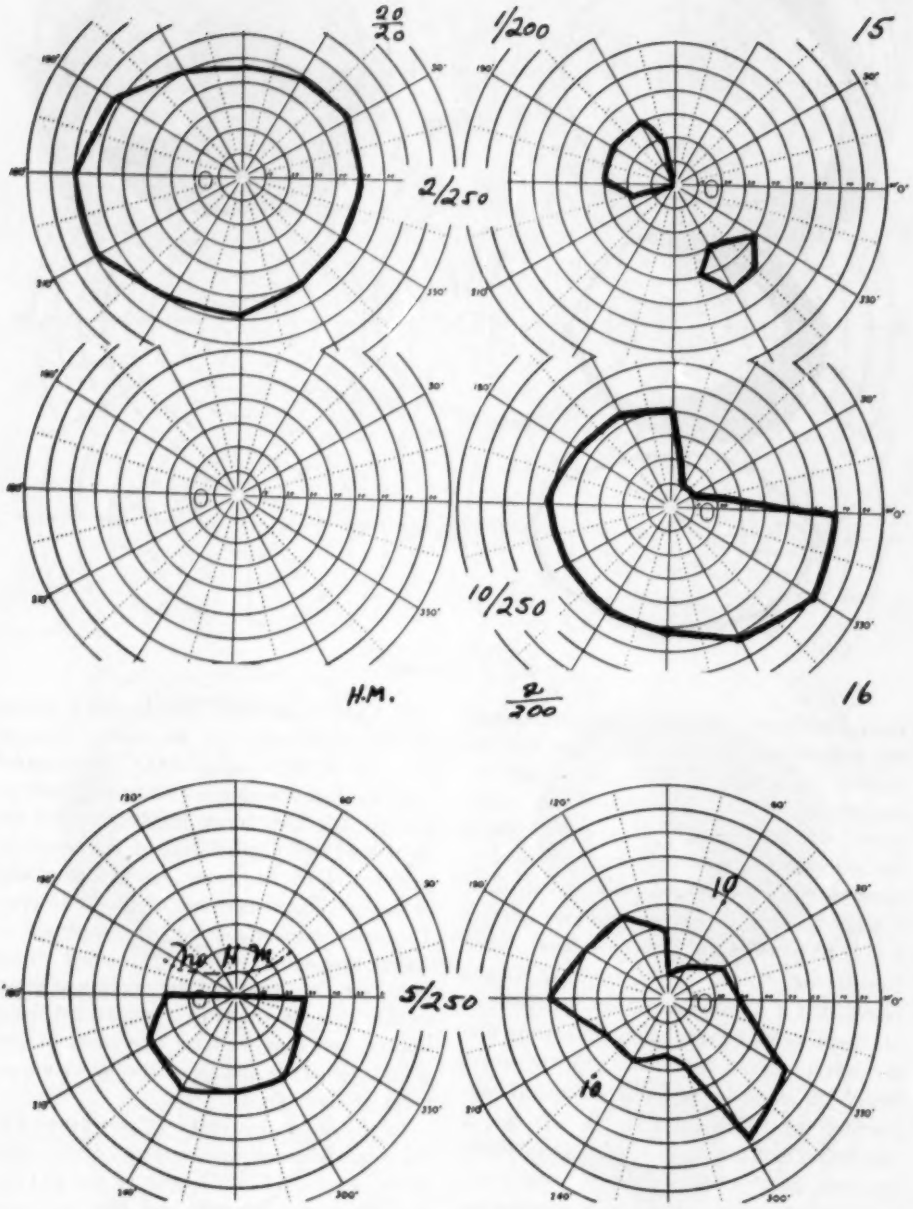
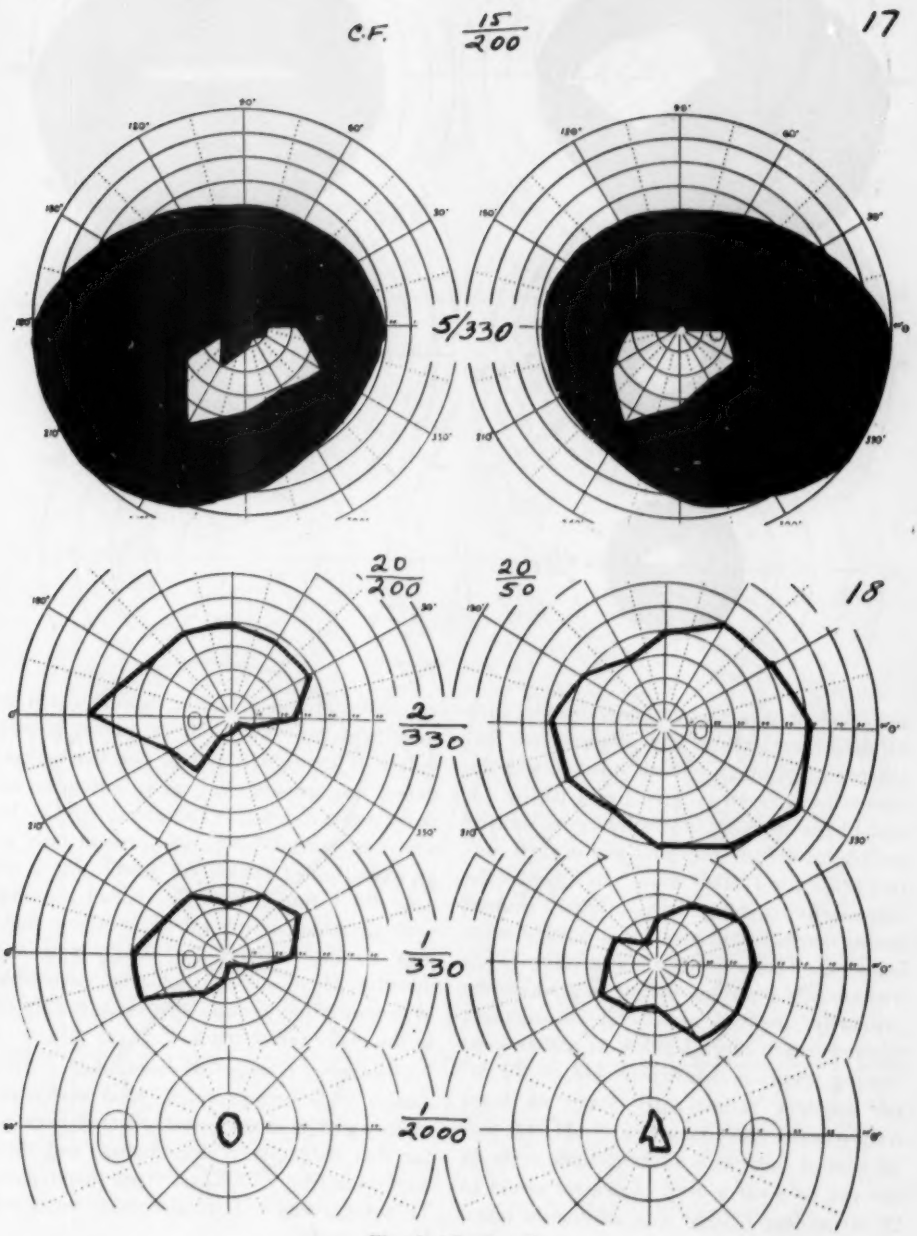


Fig. 3 (Cases 15 to 19).—Five cases of olfactory groove meningioma.



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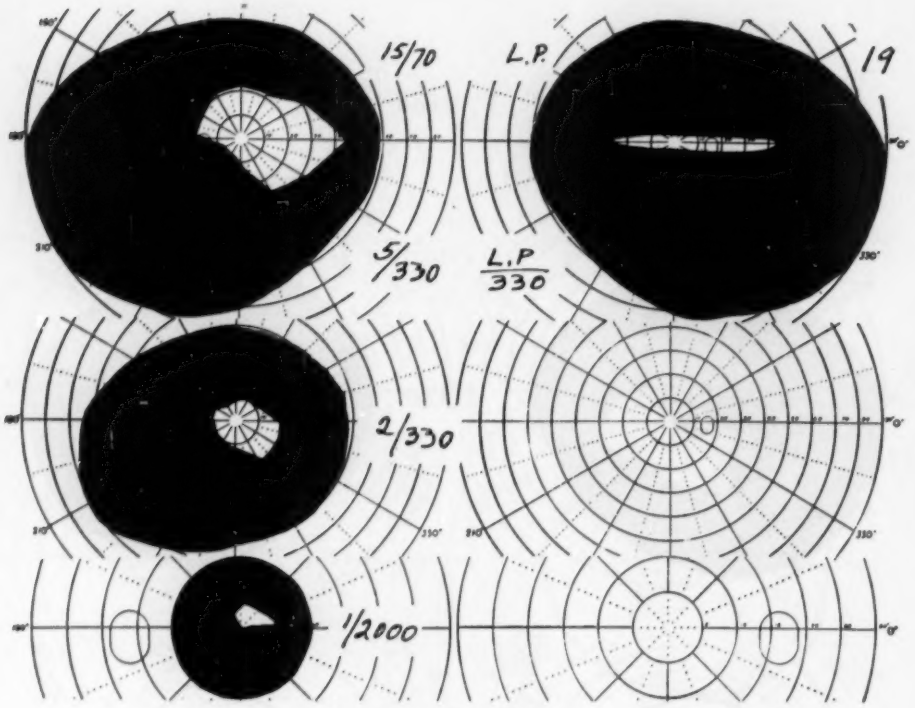


Fig. 3 (*Continued*)

involvement was always temporal. In each of these cases there was proportionate involvement of inner and outer isopters in the primarily involved eye. In Cases 10, 12, 13, and 14 the secondarily involved eyes showed peripheral defects only and had normal central fields for 1/2000 white. In Case 11 the secondarily involved eye (right) showed proportionate involvement of inner and outer isopters. These secondarily involved eyes undoubtedly represent earlier stages than the primarily involved eyes, and all of them showed intact central fields—a rather convincing proof of noninvolvement of the inner isopters at an early stage of mass compression. In Cases 5, 7, 9, 11, 12, and 14 central field was affected sufficiently in one eye to cause a drop of central vision to 20/40 or less (20/40 was arbitrarily taken as evidence of loss of central visual acuity, Snellen). However, in each of these cases the central defect was shown to be a direct extension of inner isopter defect, which in turn was an extension of outer isopter defect. Therefore, it may be said that central defect was present only as an extension of outer isopter defect. Therefore, it may be said that central defect was present only as an extension of peripheral defect, but in no case did I find a discrete central scotoma with an intact peripheral field. These findings do not support the theory that the macular fibers are particularly vulnerable to pressure due to mass compression applied to the outer nerve trunk.

Olfactory Groove Meningiomas (Five Cases).—Unfortunately, a good many olfactory groove meningiomas extend back so far that they involve the chiasm, and they were therefore eliminated from this report. Therefore, only five suitable cases remained for this study.

In Case 15 the left field was intact. In all the other eyes there was peripheral

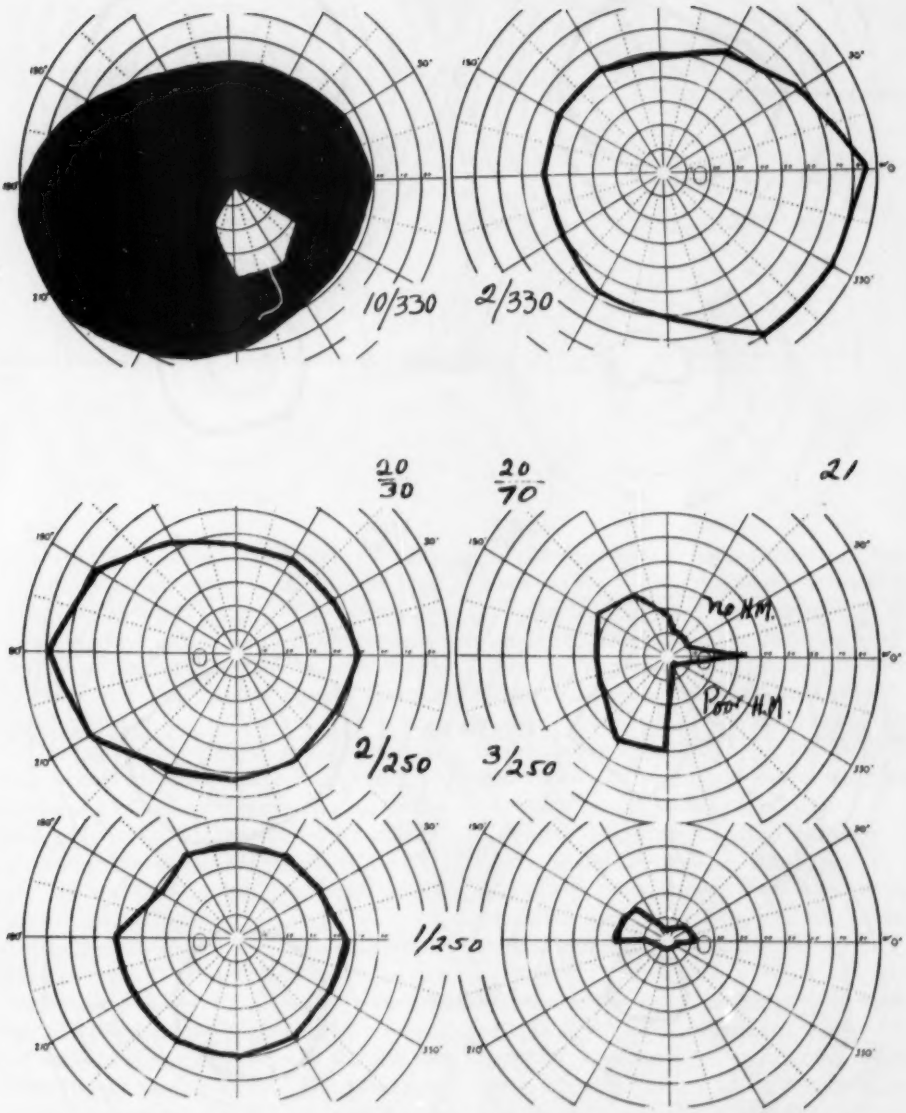
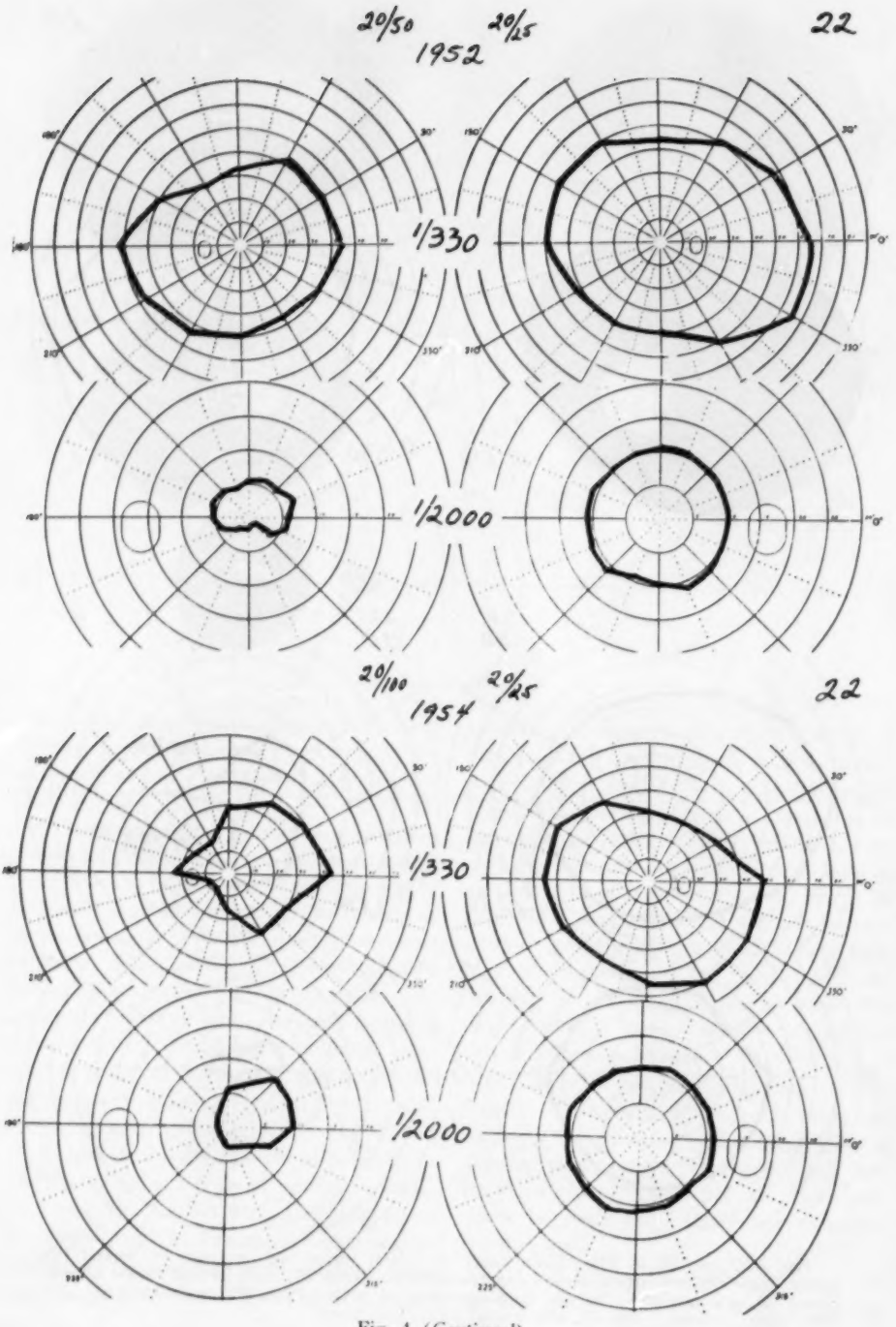


Fig. 4 (Cases 20 to 23).—Three cases of orbital tumor and one case of frontal lobe tumor. Case 20, left orbital tumor (hypernephroma). Case 21, right orbital tumor (meningioma of optic nerve). Case 22, lymphosarcoma of orbit: 1952, left field involved; 1954, both fields involved. Case 23, left frontal lobe meningioma.



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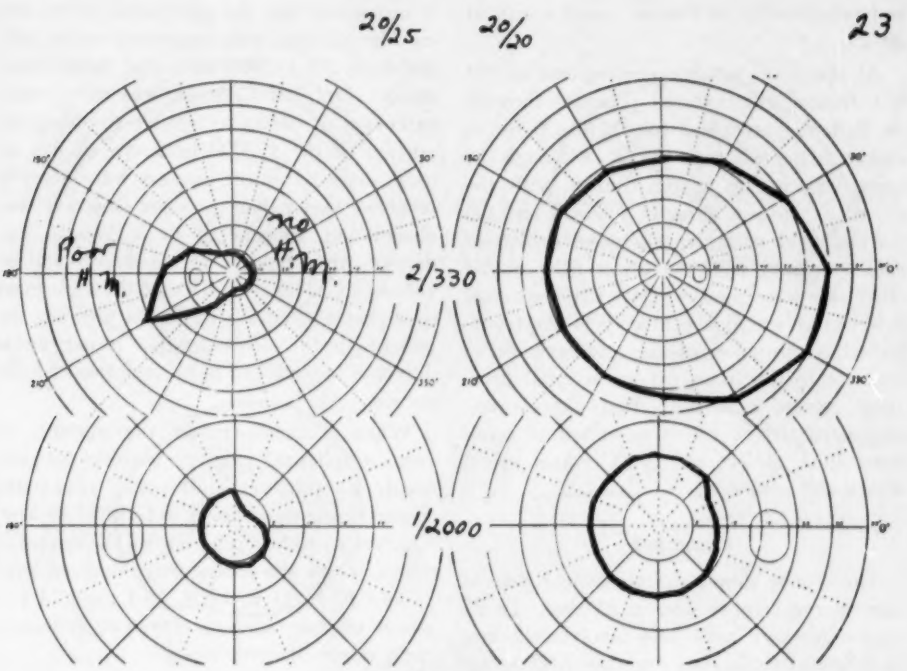

Fig. 4 (*Continued*)

involvement, tending particularly to altitudinal types of defect with proportionate inner isopter involvement and loss of central visual acuity. In no case was there central defect with an intact periphery, and certainly there was no discrete central scotoma present.

Orbital Tumors (Three Cases).—Of the three cases of orbital tumor reported here, one was a metastatic hypernephroma of the left orbit (Case 20), another was a meningioma of the optic nerve sheath (Case 21), and the third was a lymphosarcoma of the orbit (Case 22).

In Cases 20 and 21 there was proportionate involvement of inner and outer isopters in the involved eye. In Case 22, when seen in 1952, there was proportionate involvement of inner and outer isopters in the left eye with loss of central vision. The patient refused treatment and was seen from time to time until 1954, when it was found that both eyes were involved. This afforded another excellent opportunity to study the mode of field involvement in early cases of mass compression. In the case under discussion, the right field of 1954 (the secondarily involved eye) shows a definite flattening of the upper temporal peripheral field but a completely intact inner field for 1/2000 white—another example of early compression affecting the outer field and sparing the inner field. The fields of 1954 were used for tabulating results in this paper.

Central visual acuity was involved in Cases 20 and 21, and the left eye of Case 22 showed proportionate field involvement while the right eye of Case 22 (1954) showed peripheral defect only.

Frontal Lobe Tumor (One Case).—In one case of frontal lobe tumor (Case 23), with bilateral mild papilledema, there were transient episodes of blurring of vision, particularly of the left eye. Prior to operation the visual fields were recorded as shown. They showed a marked peripheral contraction in the left eye only, with a relatively slight contraction of the inner 1/2000 field

and preservation of central visual acuity of 20/25.

At operation, a large meningioma of the left frontal lobe exerted pressure through the flattened, atrophied frontal lobe tissue to compress the left optic nerve. Although the mass was not in direct contact with the nerve, its position directly above it and the marked field contracture on the ipsilateral side compared with the intact field on the other side were good evidence that the visual field defect was due primarily to the transmitted compression of the left optic nerve and not to the increased intracranial pressure. Again, as in the various other cases, peripheral defect was transmitted to cause some inner defect but good central visual acuity was preserved.

Comment

The Table shows defective field due to optic nerve compression in 33 eyes. In 25 eyes outer and inner field involvement was proportionate. In six eyes outer field defect predominated, while in only two eyes did the inner isopter show more defect than did the outer isopters. In 18 eyes the central defect involved fixation to cause a drop of central visual acuity (Snellen) to 20/40 or less. In no case was there evidence of a discrete central scotoma unrelated to a more peripheral defect, and in all cases there was some involvement of the peripheral fields.

In those eyes showing contralateral involvement from sphenoid ridge meningiomas (Cases 10 through 14) an opportunity was afforded to watch for early involvement, and it was noted that the peripheral defect was most prominent, with completely intact central fields for 1/2000 white and intact visual acuity. Only in Case 11 was there some extension of defect to involve the temporal portion of the 1/2000 field. In all five of these cases the outer isopters were actually involved sooner than the inner isopters. This observation appears to be a logical one, despite other reports of earlier central involvement. This is so because the awareness of a central defect is more apt to bring the patient to the doctor, while a peripheral defect is more likely to be unnoticed by the patient.

When a lesion crosses the midline, as from a sphenoid ridge to involve the contralateral optic nerve, it seems reasonable to expect the nasal fibers to be affected first. This seems to be borne out by the temporal defect in all the secondarily involved eyes (Cases 10 R, 11 R, 12 R, 13 L, and 14 L), which may be said to represent relatively early stages of involvement.

With increased compression, the anatomic factors such as the optic foramen edges, neighboring vessels, etc., undoubtedly cause counterpressure effect which disturbs the orderly sequence of temporal to nasal defect. At the onset, however, the simple mechanism portrayed above seems to hold true.

It may be reiterated at this point that if one is observing a patient with unilateral field defect, either for the purpose of evaluating rate of progression as a deciding factor for operative interference or for the purpose of finding contralateral involvement as corroboration of a mass lesion rather than an inflammatory lesion (retrobulbar neuritis), the temporal peripheral field of the contralateral eye is to be watched carefully. On the other hand, if the lesion is more posterior in the prechiasmal area the temporal field of the 1/2000 isopter in the contralateral eye may show changes earlier than the peripheral field.

Comparison with Visual Field Defects in Optic Neuritis.—If all mass lesions caused defects like those presented, and all cases of

Effect of Optic Nerve Compression by Mass *

Proportionate involvement (25 eyes)						
1 R	2 R	3 R	4 R	5 R		
6 R	7 R	10 R	11 R	11 L		
12 L	13 R	14 R	15 R	16 L	16 R	
17 L	17 R	18 L	18 R	19 L	19 R	
20 L	21 R	22 L				
Peripheral defect preponderance (6 eyes)						
10 R	12 R	13 L	14 L	22 R	23 L	
Central defect preponderance (2 eyes)						
8 L	9 R					
Loss of central visual acuity; 20/40 or worse (18 eyes)						
5 R	7 R	9 R	11 L	12 L	14 R	15 R
16 R	16 L	17 R	17 L	18 R	18 L	19 R	19 L
20 L	21 R	22 L				

* The numbers are the case numbers, corresponding with those in the text and Figures.

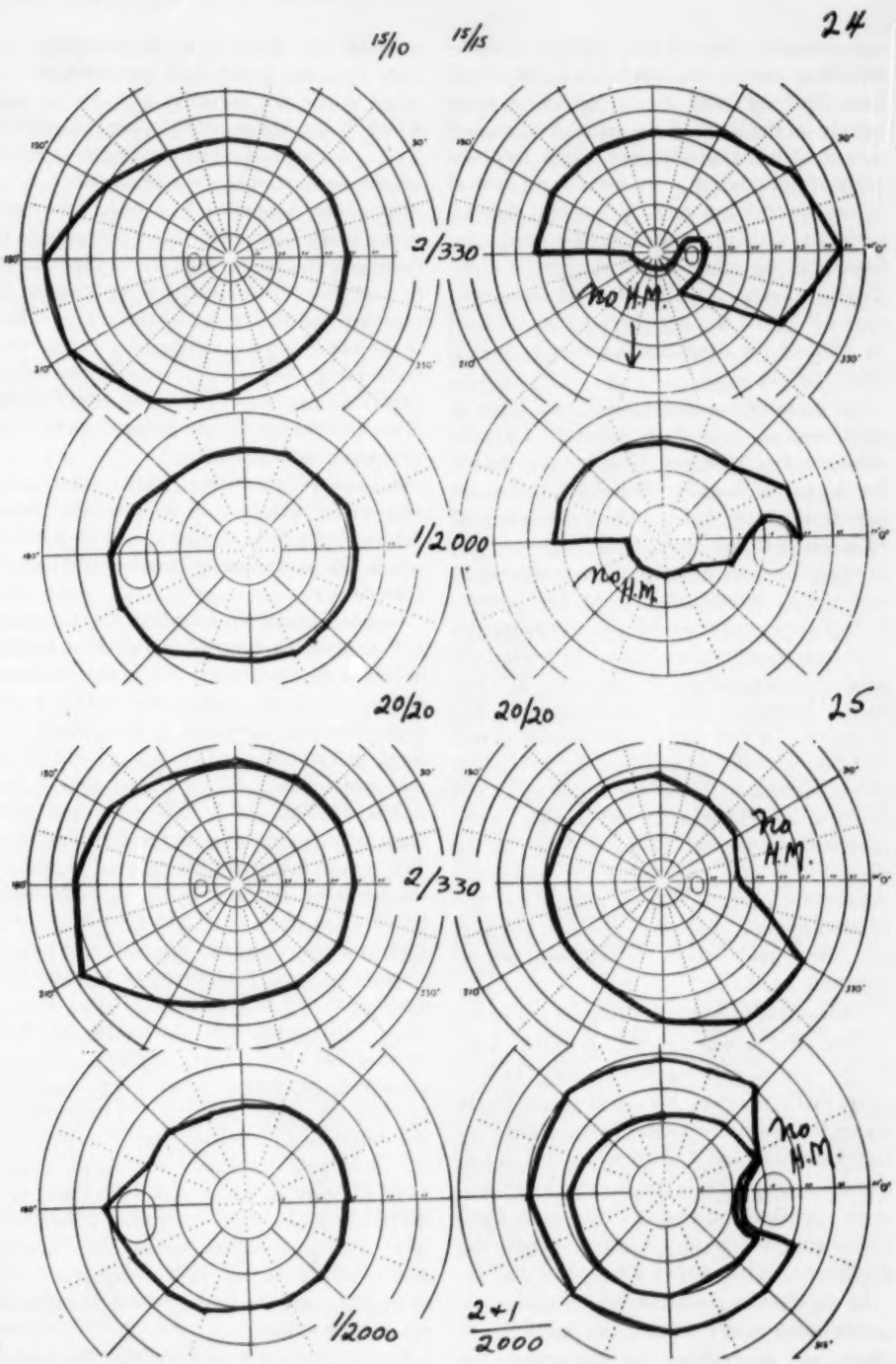

Fig. 5 (Cases 24 and 25).—Two cases of optic neuritis, showing nerve fiber bundle defect with preservation of normal central visual acuity.

optic neuritis showed only central or cecocentral scotomas, the ophthalmologist would have little difficulty in distinguishing them merely on the basis of the visual field examination. Unfortunately, the visual field defects of optic neuritis are not always central or cecocentral scotomas. Peripheral defects, with or without central involvement, are known to be more frequent than is commonly believed. In 100 cases of optic neuritis I [18] found the periphery to be involved in 24% of the cases and fixation to spared in at least 21%.

To demonstrate these points, two cases of optic neuritis have been selected. Case 24 shows a typical nerve fiber bundle defect, but it spares fixation. The sharp horizontal line in which the defect ends is characteristic of a lesion in the optic nerve, such as optic neuritis, interfering with the corresponding nerve fiber bundle above. At first glance, it may appear to resemble the altitudinal defect as seen with mass lesions like olfactory groove meningiomas, as in Case 16 (left eye). However, there are important differences. In the nerve fiber bundle defect of optic neuritis (Case 24) the horizontal defect emanates from the blind spot and skirts around fixation to end sharply in the horizontal raphe on the nasal side. In the mass lesion case (Case 16) the horizontal delineation of field has no respect for the vertical midline at all, but crosses it. This is all easily understood, of course, on an anatomic basis.

The second important difference lies in the quality of the edge of the defective field. In the case of optic neuritis (Case 24) it is seen that, whereas the field immediately above the nasal horizontal is completely intact for 2/330 and 1/2000 white, the defective area immediately below the horizontal is so completely dense that not even hand movements are seen. In other words, the defective area has a very steep edge.

In the case of the mass lesion (Case 16), on the other hand, whereas no hand movements are seen above the horizontal, the field below it is defective because it required a 5 mm. test object to be demonstrated, and even then the lower field is contracted. In other words, the defective area has an edge which is not steep but "sloping" in quality. This is the sort of effect one might expect to obtain on a simple mechanical basis, i. e., if pressure is applied to a body (the optic nerve trunk) the effect is on the outside of the trunk and transmitted to the inner layers to a degree determined by the amount of pressure and the "give" of the nerve. Thus, if the nerve is pushed against a sharp, solid body (e. g., the optic foramen) one might expect as much or even more defect in the fibers pushed against the foramen as in those in contact with the mass.

Of course, this steep edge in optic neuritis defect will be present only with dense defects, with little recovery, and in those in which the neighboring bundles are not involved.

In another case of optic neuritis (Case 25) a less frequent type of nerve fiber bundle defect is demonstrated. Here, the temporal field is involved. Again, the defect arises from the blind spot and is very dense (no hand movements). The adjacent field, on the other hand, is completely intact for 2/330, 2/2000, and 1/2000 white, thus giving a very "steep" edge to the defective area. The resemblance of this type of defect to the temporal indentation of an early mass lesion as in Case 11 (right eye) is noticed. However, in Case 11, where the defect is caused by mass compression, it is noticed again that the defective field has rather a slope to its edge—the quality of the field varying as the inner isopters are approached—in contrast to the steep edge seen in Case 25 (optic neuritis). Furthermore, the defect has no relation to or respect for the blind spot in mass compression (Case 11), whereas in optic neuritis (Case 25) the defect arises from and includes the blind spot as a part of the nerve fiber bundle defect. This is all easily explained, of course, because of the different anatomical factors involved.

I have attempted to show that the visual field changes of mass lesions show peripheral

field changes before involving the fixation area. On the other hand, I have shown that while in most cases of optic neuritis cecocentral defects predominate, in many others peripheral defects which spare fixation may be seen. Therefore, such peripheral field defects in optic neuritis may confuse the visual field picture with that of a mass lesion, although certain diagnostic differences are pointed out.

General Summary

In view of all the above data, the following conclusions seem to be reasonable:

1. The truly discrete "central" scotoma which occurs as a result of mass compression of the optic nerve is probably not nearly as frequent as the literature seems to imply. Even when reported in the recent literature, such truly central scotomas seem to be highly elusive, or of a very transient nature, and early break-through to the periphery has been stressed.

2. In my experience, mass compression of an optic nerve well in front of chiasm causes peripheral defect in the visual field, with accompanying or subsequent central involvement as a direct extension of the peripheral defect. While proportionate involvement of outer and inner isopters was found in most cases (25 out of 33), predominately peripheral involvement was found more frequently than predominately inner involvement (6 as compared with 2 out of 33). However, in no case could I find a completely normal periphery with a distinct central scotoma.

3. The use of proper visual angles in testing the periphery is most important in evaluating these field defects. One must avoid the use of excessively large visual angles in testing the peripheral field for involvement. As a matter of fact, at times it may be necessary to use minimal visual angles and minimal techniques such as rapid comparisons and "simultaneous stimulation" to bring out peripheral defect or break-through to the periphery.

4. It is possible that a good many of the early peripheral defects are not recorded because the patient is not apt to notice them and therefore does not seek attention until the central field is involved.

5. The early temporal field defects which I found in contralateral involvement from sphenoid ridge meningiomas are well known in the literature. They serve as a basis for estimating rate of growth and extension of a tumor from the opposite side. The clinical importance of such early temporal defect is twofold: (*a*) It helps to establish a diagnosis of mass lesion as differentiated from optic neuritis. (*b*) It furnishes criteria which would help the neurosurgeon to decide whether or not to risk surgery on an elderly patient or on one in whom the surgical risk is great. The alternative is to lose vision at a rate shown by the visual field findings.

From the point of view of this paper, this well-established early temporal field involvement only serves to substantiate the early effect of mass compression on the optic nerve as being a primarily peripheral defect.

6. It appears from the evidence presented that the visual field defects due to mass compression of the optic nerve may be explained on the simple mechanical basis of direct pressure transmitted through the nerve trunk, and involving outer and inner fields, without invoking any special vulnerability of the macular fibers—at least, not to pressure.

7. An altitudinal defect ending at the horizontal line may be seen in both optic neuritis and mass compression. However, in optic neuritis, if it happens to spare fixation, the defect will emanate from the blind spot, skirt around fixation, and end on the nasal horizontal, and in cases of dense defect with little recovery the edge of the scotoma is apt to be very "steep." In mass lesions, on the other hand, the altitudinal defect is not apt to respect the vertical midline and bears no particular relationship to the blind spot. Furthermore, the edge of a defective area due to mass compression is much more likely to be of a sloping nature.

8. Finally, while some visual field criteria have been presented to help differentiate the field defects of mass compression from those of optic neuritis, the similarities that exist in the two types of field have also been shown to be a potential source of confusion.

For this reason, one cannot rely on visual fields alone in differentiating between mass compression and retrobulbar neuritis. Certainly, all other clinical modalities must be utilized, particularly a thorough, painstaking history, always a very reliable tool in making a differential diagnosis.

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Bilateral Papilledema in Otherwise Well Patients

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The ophthalmologist is frequently called upon to evaluate a case in which bilateral papilledema is the only finding. Information concerning such a condition is abundant in neurological and neurosurgical journals, but relatively little has been written in the ophthalmological literature. It is, therefore, the purpose of this paper to review the available information; discuss the etiology, differential diagnosis, and treatment of this disease, and add a detailed report of a further case.

Briefly, the syndrome is manifested by a patient who feels generally well, may have an occasional headache, may complain of blurred vision, and may have tinnitus, vertigo, or dizziness. Diplopia and abducens palsies may occur.[1] General physical examinations are negative. Papilledema, most generally bilateral, is present and reaches from 2 to 5 or 6 D. Hemorrhages and exudates on and near the optic nerve head are frequently present. There are no ventricular abnormalities, focal neurological signs, or disturbances of awareness or intellect.

The syndrome has been known under several names: (1) benign intracranial hypertension,[2,21] (2) pseudotumor cerebri,[3, 5,21] (3) serous meningitis,[4,8] (4) generalized cerebral arachnoiditis,[3] (5) meningoencephalitis serosa,[5] (6) serous effusion of inflammatory origin,[5] (7) generalized cisternal arachnoiditis,[5] (8) otitic hydrocephalus,[6] (9) toxic hydrocephalus,[7] (10) papilledema due to intracranial venous obstruction,[8] and (11) meningeal hydrops.[9]

Received for publication Feb. 1, 1957.

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Review of the Literature

Quincke[4] first described this syndrome in which cases of increased intracranial pressure are associated with clear cerebrospinal fluid. He attributed the disease to otitis media, head injury, over-work, alcoholism, or influenza. He considered the condition to be a benign form of meningitis with excess cerebrospinal fluid excreted by the choroid plexus. Symonds[6] suggested that these cases be called "otitic hydrocephalus." He considered the condition to be a complication of otitis media without the existence of a cerebral abscess. His terminology, he felt, implied no active progress of inflammation and included the fluid within both the ventricles and the subarachnoid space. Later[10] he felt that infection of the lateral sinus played an important part in the causation of otitic hydrocephalus but that obstruction of the lateral sinus per se was not the essential factor.

In 1952 Symonds[11] further enlarged on his theory that obstruction of the intracranial sinuses plays an important part in the development of this syndrome. He felt that thrombosis in intracranial veins may occur from the direct spread of extracranial infection without fever or other constitutional disturbance and that the infective focus may be of trivial proportions.

Woodhall[12] reported a case of a young girl with symptoms of increased intracranial pressure, papilledema, without localizing signs, in which the diagnosis of thrombosis of a lateral sinus was made.

Davidoff and Dyke[8] presented a series of cases of "serous meningitis" in relatively young patients. The outstanding symptoms were headache and failing vision. The duration of symptoms was six months or less.

Dandy[13] reported 22 cases. In addition to the usual findings, hemorrhages in the

retinae were common. These were generally multiple and scattered over and beyond the discs. Enlarged blind spots, scotomata, or blindness was present in 50% of the cases.

McAlpine [7] preferred the term "toxic hydrocephalus" to "otitic hydrocephalus" and included not only "otitic" but nasopharyngeal and other sources of infection.

Frazier [5] reported the pathological findings at autopsy in several cases of "pseudotumor cerebri."

Ford and Murphy [14] presented a clinical analysis of several types of increased intracranial pressure, including that due to thrombosis of the dural sinuses and "brain swelling of unknown origin."

In discussing papilledema due to intracranial venous obstruction, Pennybacker [20] stated that, while in these cases the fundi may cause alarm, he had never seen a case of serious visual failure from secondary optic atrophy.

Meredith [15] states that should headache be present the burden of proof is on him who argues for a (brain) tumor in any given case. In cases of "pseudotumor cerebri" he feels that operative relief is important to prevent serious impairment of vision.

Ray and Dunbar,[16] on the basis of x-ray studies following the injection of radiopaque material, were able to demonstrate a block in the superior longitudinal or lateral sinuses.

Giller and Cogan [9] presented seven cases. They feel that the ophthalmologist must play an important part in the management of cases of papilledema due to "meningeal hydrops." He must carefully observe the patient for signs of increasing papilledema, decreasing visual acuity, and loss of visual field.

Most recently, Bradshaw [2] has presented 42 cases which, he feels, fall into five categories by virtue of their associated pathology: (1) infection of the second branchial cleft and respitory tract, 61%; (2) extracranial venous thrombosis, 10%; (3) obesity, 14%; (4) post-traumatic condition, 5%; (5) undetermined, 10%. He believes that the term "otitic hydrocephalus" is clearly unsuitable, since infections of the second branchial cleft are not exclusive in the production of this syndrome. Also, most clinicians, in speaking of hydrocephalus, imply dilation of the cerebral ventricles. This is not a feature of the syndrome.

Etiology

Attempts to establish the etiology in these cases have led to widely varying results. This probably accounts for the multiplicity of names for the syndrome which abound in the literature.

Numerous contributing factors have been named by various authors. Nonsuppurative inflammations of the nasopharynx [17]; puerperal thrombosis of the leg veins, peritonsillar abscess, thrombophlebitis migrans, and frontal sinusitis [10]; trauma, chachexia, and anemia [18]; cardiac disease, postoperative and post-traumatic states, hyperpyrexia, hemorrhage, and rare blood dyscrasias,[19] and head injury, over-work, alcoholism, and influenza [4] have all been implicated.

There seems little disagreement that the ultimate factor which produces the papilledema is an increase of the intracranial pressure. Normally, the pressure is maintained by the balance between the formation of cerebrospinal fluid and its absorption into the blood stream. Increased production or decreased absorption produces a rise in cranial pressure, much as in the production of glaucoma.

Whatever the predisposing factors, most authors are in agreement that an intracranial venous thrombosis is generally involved. Thrombosis of one lateral sinus, in the absence of bacteremia, as a rule causes no symptoms at all unless it happens that the other sinus is absent or very small. In these circumstances occlusion of the lateral sinus obstructs the main effluent channel of the intracranial circulation.[11,14] Ray and Dunbar [16] have demonstrated photographically the existence of thrombosis in the lateral or longitudinal sinuses in four patients.

Dandy[13] reasoned that the intracranial pressure is dependent upon the intracranial fluid content—either blood or cerebrospinal fluid—otherwise, rapid changes could not occur. He felt that the fluid was in the brain tissue per se, since evacuating fluid from the subarachnoid space did not relieve the pressure and since the ventricular system was generally small. Dandy doubted the existence of obstruction of the big venous sinuses since, in his cases, the Queckenstedt test was never positive.

Pathology

Pathologic material is rare. Patients do not die from this syndrome, so it is only by fortuitous events that material has come to the microscope. Frazier[5] reported his finding to be mild inflammation of the meninges, changes in the cerebral nerves (neuritis, perineuritis, and interstitial changes), lymphocytic infiltration of the pia, and proliferation of the lymphocytes in the perivascular spaces, enlarged glial cells, and thickening of the vascular walls. Marked changes were noted in the cells of the choroid plexus, some being completely destroyed, some enlarged or swollen, and others without nuclei, while in some, several nuclei could be distinguished.

Diagnosis

This syndrome must be thought of in any case presenting bilateral papilledema without localizing neurologic signs. The papilledema is generally from 1 to 4 D. but may reach as high as 6 D. Hemorrhages scattered on and around the swollen discs are common. Headaches and decreasing vision accompany almost all the cases. The intracranial pressure is elevated, though frequently not as greatly as one would suspect from the degree of papilledema present.[2] The cerebrospinal fluid is generally normal, although Giller and Cogan[9] reported three cases out of seven with slightly elevated cerebrospinal fluid protein. Pneumoencephalograms reveal normal or slightly diminished ventricles. Awareness and intellect are intact. Diplopia, tinnitus, and abducens palsies are noted occasionally.

The syndrome is more than twice as common in females as it is in males.[1] The duration of symptoms varies from two to six months and may be several years.

Visual field studies show central defects, progressive concentric constriction due to classical secondary optic atrophy, homonymous quandrantic defects, enlarged blind spots, and slight general depression.

The loss of vision may progress to complete blindness in one or both eyes. The process spontaneously resolves, leaving visual impairment proportional to the amount of optic atrophy present.

Differential Diagnosis

Conditions which must be differentiated from papilledema due to "benign" increased intracranial pressure are dural sinus thrombosis, encephalitis, fungus infection, cerebrovascular disease, and demyelinating disease.[3] Brain abscess, tumor of the posterior fossa, and arachnoiditis of the posterior fossa must be considered.[5] Malignant hypertension, polycythemia vera, blood dyscrasias, emphysema, and chronic idiopathic hypoparathyroidism must be ruled out.[1]

Treatment

Once the diagnosis is established the ophthalmologist must determine the course of therapy. Since the disease is self-limiting, the only concern may be for the status of the vision. Should the papilledema be of moderate degree, the visual field change minimal, and secondary optic atrophy absent or slight, "watchful waiting" is in order. Most authorities agree, however, that should the vision be impaired operative interference is indicated. Mechanical decompression then becomes a necessity in this, a visual emergency. Dehydration measures and repeated spinal taps are generally not sufficient.

Report of a Case

A 26-year-old rather obese white woman was first seen on Dec. 10, 1955, because of

blurred vision and vague fronto-occipital headaches which had been present for about two weeks. Three weeks previously she had had a severe cold. The patient did not wear glasses. There was no history of previous difficulty with her eyes, and she had not been previously subject to headaches. The system review was negative, as was the family history.

Examination showed the visual acuity to be right eye, 20/200; left eye, 20/25. The lids, conjunctivae, sclerae, and corneas were normal. The pupils each measured 3 mm., were round and regular, and reacted normally to light and in accommodation. Slit-lamp examination was negative. The intraocular tension measured 17 mm. of mercury in each eye. The extraocular muscle function was normal.

Ophthalmoscopically there was marked bilateral papilledema. The right disc was swollen 5 D. There were numerous superficial hemorrhages scattered on the surface of the disc and in the neighboring retina, with a linear hemorrhage just nasal to the macula. The veins were markedly dilated. Hard, glistening white exudates were seen adjacent to the disc temporally. The left eye showed a similar picture, with 6 D. of papilledema. In addition, there was an accumulation of soft white exudates in the macular area similar to a "star" formation.

Examination of the visual fields revealed a greatly enlarged blind spot of the right eye, extending almost to fixation. The blind spot of the left eye was almost twice the normal size.

On the following day the patient was hospitalized for a diagnostic work-up. Blood pressure on admission was 175/110 mm. of mercury. There was tachycardia (heart beat, 120 per minute). The patient weighed 205 lb. (92.25 kg.) (she was 5 ft. 6 in. [165 cm.] tall). The general physical examination was otherwise negative. Neurological examination failed to reveal localizing signs or abnormalities. The patient was alert and did not feel ill beyond apprehension.

The red blood cell count was 4,670,000 cells per cubic millimeter, with 90% of hemoglobin. The white blood cell count was 8300, with a normal differential count. The Addis count and a creatinine-clearance test were normal. Urinalysis was not remarkable. A serologic test for syphilis was reported as negative. Serum albumin, globulin, total protein, nonprotein nitrogen, and glucose were all reported as normal, although the total cholesterol was 306 mg. per 100 cc. (normal, 150-250 mg.). A lupus erythematosus blood preparation was negative.

On advice of the consulting neurosurgeon, a lumbar puncture was not done.

An electroencephelogram was interpreted as normal, as were an electrocardiogram, chest x-ray, skull x-rays, and intravenous pyelograms. Ventriculography was done via biparietal burr holes. The operator reported the brain substance to be stretched tightly beneath a normal dura. The ventricular system was reported as within normal limits. The cerebrospinal fluid analysis showed a negative Pandy test, normal cell count, and slightly lowered protein content.

Several days after admission the blood pressure returned to 140/70. The blood pressure has remained normal ever since. Tests for pheochromocytoma were negative.

Eleven days after admission the patient was discharged without the etiology of the increased intracranial pressure or the papilledema having been determined. During the hospital stay the right macula developed a "star" formation, but the fundi were otherwise unchanged.

On Dec. 23, 1955, the visual acuity was right eye, 20/80; left eye, 20/30. The papilledema had decreased 3 D. in each eye. There were fresh tiny hemorrhages on the surfaces of the discs. The visual fields were unchanged except for a slight increase in the size of the left blind spot.

The blind spots gradually decreased in size along with a gradual increase in the visual acuity. On Jan. 30, 1956, a relative pericentral scotoma appeared in the right eye, and this disappeared by the end of

Fig. 1.—Right eye of patient three months after onset of symptoms. Optic nerve head is flat, with glial scar tissue partly obscuring the margin. Radial striae from edema are seen in the posterior pole.

February. The visual acuity returned to right eye, 20/25; left eye, 20/20, and the patient remained asymptomatic.

On the last examination, nine months after the onset of symptoms, there was no papilledema. There were glial "scars" on both discs, and the disc margins were markedly irregular. The hemorrhages had disappeared, but there were numerous small hard white exudates in the posterior poles (Figs. 1 and 2).

Comment

The case presented here represents another example of the syndrome of bilateral papilledema and increased intracranial pressure without expanding lesions or other cranial abnormalities.

In attempting to classify this case as to associated pathology, the patient fits most closely the third type of Bradshaw.[3] He found 6 of 61 cases (14%) to have obesity as the only abnormal finding. It was reasoned that it was not uncommon to find a moderate elevation of lumbar cerebrospinal fluid pressure in obese but otherwise healthy persons. This is due to the pressure exerted by the thighs and abdominal fat on the lumbar veins when the person is in the lateral

Fig. 2.—Left eye of patient three months after onset of symptoms, showing glial scar tissue on the optic nerve head and residual of exudates in the macular area.

position usually employed for lumbar puncture. In Bradshaw's series all the patients in the obese category were women. He thought that perhaps there might be a factor of endocrine disfunction here associated.

The benign course was compatible with a thrombosis of a dural sinus. The onset may well have represented the actual occurrence of the thrombosis. The original absorption channels were reestablished or new ones became sufficient before irreversible damage was done to the optic nerves.

The history of a severe head cold three weeks before the first visit suggests that possibly the condition known as otitic hydrocephalus may have occurred. It is known that the infective focus may be minor and that a full-blown case of otitis media is not necessary for the production of the syndrome.

The remarkable visual recovery in this case was achieved because secondary optic atrophy did not occur or only developed to a minimum degree. It was my impression that the course of this disease from onset of symptoms to return of vision was shorter than the average of the cases reported in the literature. The amount of secondary optic atrophy present is probably roughly proportional to the degree of elevation of the discs and the duration of the elevation. The papilledema in this case started to decrease within one month after the onset of the symptoms and was completely gone in three months.

This case illustrates the thesis that the syndrome is self-limited and its outcome is generally favorable. While some would advocate immediate decompression, a more moderate course in which the status of the vision is the guidepost seems to be indicated. None would disagree, however, that should vision be endangered operative interference is necessary. The oftentimes difficult task of determining just when the danger point has been reached belongs to the ophthalmologist.

Summary

Bilateral papilledema as a result of benign increased intracranial pressure is discussed. The literature is reviewed, and the present status of information regarding the etiology, pathology, diagnosis, clinical course, and differential diagnosis is presented.

A detailed report of a case is presented in which the visual outcome was favorable in spite of the marked papilledema originally present.

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Further Studies on the Incidence of Antibiotic-Producing Micro-Organisms of the Ocular Flora

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The possibility that inhibitory organisms of the "normal" microflora of superficial human tissues may be significant in resistance to or recovery from infections in these areas was suggested many years ago.[1-3] Until the recent expansion of our knowledge with regard to antibiotic substances, such studies were usually somewhat indeterminate. Reexamination of the problem since that time has shed much light on the prevalence and characteristics of such antibiotic-producing organisms and has provided much circumstantial evidence implicating them in resistance or recovery mechanisms. The antibiotic activities of the microflora have been especially studied in the intestinal tract [4-9] and in the ocular flora.[10-13] In addition, such behavior has been found to be frequent in the organisms of the nose and throat,[14,15] oral cavity,[16,17] and skin.[18-20] Numerous antibiotics seem to be involved,[3, 21-24] and many of them seem to be of polypeptide nature. These antibiotic properties of the normal flora may also be of much importance in the superinfections found during intensive antibiotic therapy. This has been strikingly suggested by the experimental studies of Seiburth et al.[25] and by the observations of Bohnhoff et al.[26] and Freter.[27] The latter two investigators were able to infect experimental animals by the oral route with Salmonella organisms or cholera vibrios when the "normal" flora was suppressed with antibiotics.

In the previous reports from this laboratory [10-13] the ocular microflora was studied rather intensively. Antibiotically active staphylococci (the predominant species in the ocular flora at the present time) were found to be rather numerous and prevalent. The antibacterial spectra of a sample of these strains, as well as some characteristics of the antibiotics involved were examined in some detail. As one approach to the assessment of the ecological significance of such organisms, experimental mixed infections of mice have suggested the in vivo importance of such inhibitory properties.[28] Studies with partially purified antibiotic of one strain, chosen more or less at random, have shown it to be an agent of rather low toxicity, with a high degree of prophylactic activity in mouse Clostridium septicum infections, one of the bacterial species very sensitive to these substances.[13]

With regard to more direct data obtained in the human, a previous report failed to show any significant differences in the incidence of antibiotic strains in persons with normal eyes and those with conjunctival inflammations of diverse etiologies. In this latter study, two staphylococcal strains were used as indicator organisms. As the antibacterial spectra were worked out, it became apparent that indicator strains of other species might reveal a much greater incidence of antibiotic properties among these organisms than were found previously. Since the corynebacteria as a group proved to be exquisitely sensitive, after orienting tests a strain of Corynebacterium pseudodiphtheriticum was used as one indicator in the present

Received for publication Jan. 15, 1957.

This work was supported by a grant (G 3801) from the Division of Research Grants of the National Institutes of Health, Public Health Service.

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report, as well as a strain of Micrococcus pyogenes var. albus (Staphylococcus albus) employed in the previous study. It was hoped that use of this more sensitive indicator might reveal significant differences in the incidence of antibiotic producers among patients with normal conjunctivae, as compared with those with infected eyes. This type of finding was obtained among persons with and without shigellosis in other studies.[8,29]

Materials and Methods

The ocular conjunctival and lid cultures were taken according to techniques used at the Institute of Ophthalmology, Presbyterian Hospital.[30] From each patient, samples of about 20 isolated colonies were transplanted from the primary blood agar culture to fresh plates prepared from proteose No. 3 agar (Difco). These colonies were chosen so as to represent approximately equal numbers of strains from the conjunctivae and lid margins, and sampling colonies of slightly varying appearances was attempted. In many instances Gram stains of such colonies demonstrated them to be Gram-positive cocci in random clumps. On the basis of previous data,[11] most of them were assumed to be S. albus strains. After growth overnight at 37 C, the sampled colonies were stored in the refrigerator until assayed for antibiotic activity. Previous observations had demonstrated that such properties are usually highly stable under these conditions for long periods of time, even years. The accumulated strains for each month's cultures were freshly grown and then assayed at one time for inhibitory properties against the C. pseudodiphtheriticum, Strain A 6485, and the strain of ocular S. albus 7-6 used previously. The indicator organisms were uniformly seeded on the surface of proteose No. 3 agar plates and the test organisms were spot inoculated, as described in earlier reports. Inhibition zones were measured as the distance from the edge of the test colony to the beginning of normal growth of the indicator organisms. In those instances where attempts were made to produce crude antibiotic solutions, the organisms were grown on the surface of soft proteose No. 3 agar and the fluid was harvested by freezing and thawing. This technique and the assay method have also been described previously.[11] All of the crude centrifuged liquors were heated at 70 C for half an hour to destroy any remaining organisms.

The patients utilized for this study represent persons referred to the diagnostic laboratory of the Institute of Ophthalmology for bacteriological study. They included those with essentially normal conjunctivae who were having preoperative cultures taken[30] as well as those with all types of superficial ocular infections and inflammatory reactions. They were predominantly adults in the older age groups, although cultures were made for a few younger persons also. Both sexes were included approximately equally. In some instances repeat cultures were taken within a few days or weeks. In addition, antibiotic preparations were administered locally to some of these patients.

From a small group of persons, cultures were also taken from the anterior nares, as well as the ventral surface of the hand. These were also obtained with broth-moistened swabs streaked onto blood agar plates.

The entire study lasted two years and two months. During this period 24,389 strains from a total of 1092 different patients were examined for their antibiotic activity. An average of approximately 45 patients were sampled each month. Twenty-nine persons were reexamined on two visits at intervals of one or more months.

Results

The types of inhibitive effects obtained were similar to those found previously. In view of the great frequency of antibiotic activities that were found, Figure 1 is shown to represent a sample of the plates that were observed during a period of high incidence. It must be stressed that the colonies on each plate represent random-

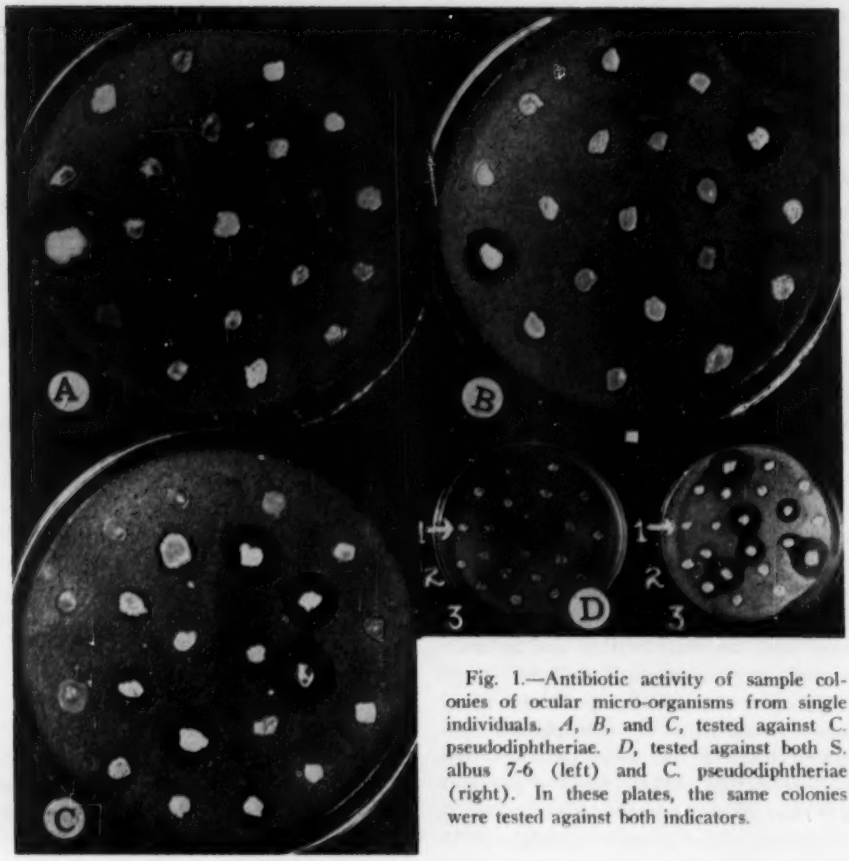

Fig. 1.—Antibiotic activity of sample colonies of ocular micro-organisms from single individuals. *A*, *B*, and *C*, tested against C. pseudodiphtheriae. *D*, tested against both S. albus 7-6 (left) and C. pseudodiphtheriae (right). In these plates, the same colonies were tested against both indicators.

sampled strains from a single patient. It can readily be seen that the flora of each patient may contain several different kinds of antibiotic producers, as well as nonactive strains. The concentration of active organisms in each patient was also variable, in some instances all the sampled colonies showing the same behavior. In addition, Figure 1*D* shows clearly the difference in susceptibility between the corynebacterial and the staphylococcal strains.

While most of the active organisms produced zones of complete inhibition of the corynebacterial strains, about 10% of the active strains produced only partial inhibition in the affected zones. Such partial effects were more frequent with the staphylococcal indicator, but, unless otherwise indicated, these organisms were not included in the results as antibiotic-producers.

During the two-year period, of the 24,389 strains tested, 11,413 (47%) showed activity against the C. pseudodiphtheriticum strain, with clear inhibition zones equal to or greater than 0.1 mm. A total of 7261 (30%) revealed zones greater than 1.1 mm.; 2977 (12.2%) had zones greater than 2.0 mm., while 682 (2.8%) produced areas larger than 4.1 mm. in width. Because of the surprisingly high percentages of strains that

were active, it seemed most important to rule out the possibility of nonantibiotic mechanisms of inhibition. Accordingly, a series of crude supernates were prepared according to the procedures used earlier, and these were assayed after heat-killing residual organisms at 70 C for 30 minutes. Thirty-two highly active, twenty-nine slightly active, and twenty nonactive strains from different patients were tested in this way. The former group were those producing inhibition zones of 2.5 mm. or more against either the staphylococcal or corynebacterial strains (or both), while the slightly active organisms produced clear zones less than this. Of the 32 highly active strains, all but 3 produced rather potent crude antibiotic supernates rather readily. Of the 29 slightly active organisms, 13 produced crude antibiotic of rather low titer, while none of the 20 nonactive strains showed inhibitory activity of the crude preparations. These data are of the same pattern as found previously and strongly indicate that the extremely frequent inhibitions observed here were also due to antibiotic substances. As a further check on this, and to obtain some indication as to the chemical nature of the agents produced, 31 of the crude antibiotics were tested for trypsin destructibility. The techniques used were the same as in a previous report. It was found that 17 of the antibiotics were completely destroyed by this crystalline enzyme, 2 were partially destroyed, and the remaining 12 were unaffected. This also is very similar to earlier results [11] and points to the peptide nature of the majority of these substances.

That the corynebacterial indicator was much more highly sensitive to these agents

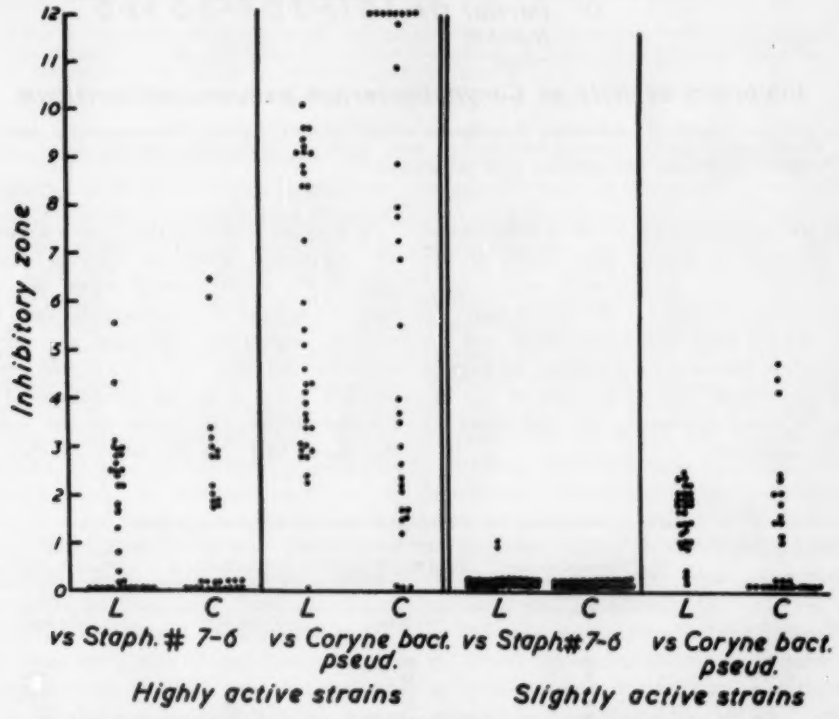

Fig. 2.—Production of crude antibiotic solutions by sample strains of inhibitory ocular organisms. Each point represents the value obtained with one organism. *L*, inhibition zones (in millimeters) in tests with the living antibiotic-producing strain. *C*, inhibition zones in tests with crude antibiotics from these strains.

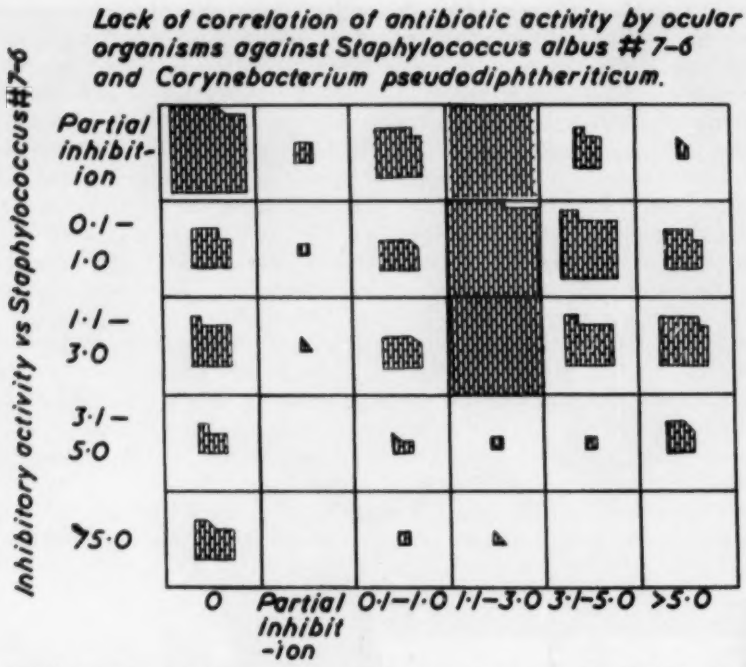

Fig. 3.—Lack of correlation of antibiotic activity against the two indicators, with ocular staphylococcal strains showing inhibition of both. Each of the smallest squares seen in any category represents data obtained with two strains.

than the staphylococcal strain is emphasized by the over-all finding that 10,503 of the 11,413 antibiotic strains were active only against the former. Of the 910 strains active against both indicators, there was no correlation between these effects. In Figure 3 is represented the comparison of the inhibition zones against the two indicators by these organisms.

It may be seen that there were a number of organisms active to varying degrees against the staphylococcal strain but quite inactive against the corynebacterium. Conversely, organisms inhibiting the corynebacterial indicator to 1.1-3.0 mm. might produce only a partial inhibition of the Staphylococcus. It seems almost certain, therefore, that, on the basis of this and

TABLE 1.—*Incidence of Antibiotic-Producing Micro-Organisms*

Period	% of Persons Carrying Antibiotic-Producers Active Against Corynebacterium	Total % of Strains Producing Inhibition of C. Pseudodiphtheriticum		Total % of Strains Active Against Staph. 7-6,
		>0.1 Mm.	>2.0 Mm.	>0.1 Mm.
1- 3/52	97	67	27	2.7
4- 6/52	85	43	7	1.0
7- 9/52	90	54	15	2.0
10-12/52	80	42	13	7.1
1- 3/53	78	40	11	4.8
4- 6/53	80	36	9	3.2
7- 9/53	75	44	10	2.0
10-12/53	72	39	9	5.7
1- 2/54	78	43	8	2.3

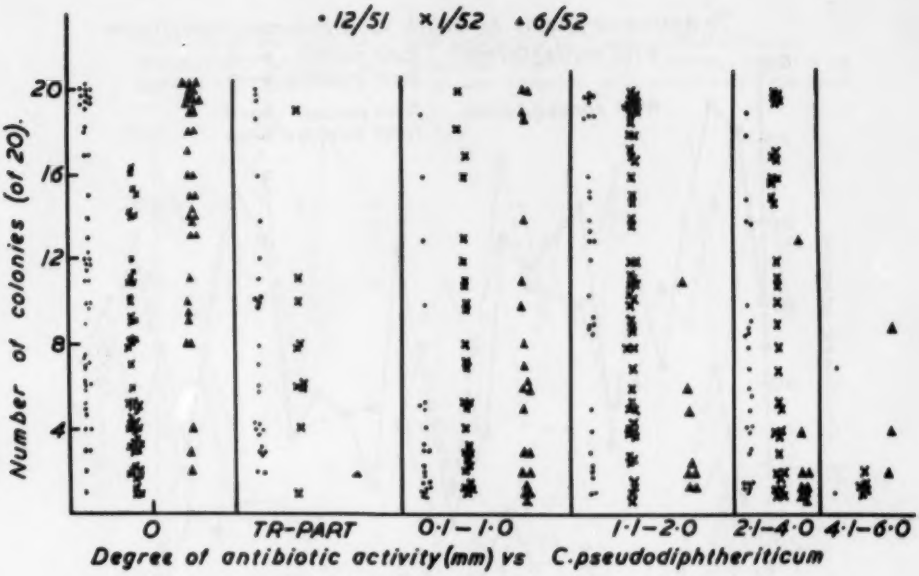

Fig. 4.—Incidence of organisms of varying antibiotic activities in single individuals during three sampling periods. Each point represents the number of strains of a given activity from one patient from the sample of 20 taken from that person.

previous information, a large number of distinct antibiotic substances are involved.

With regard to the variations in incidence of such organisms in the patients sampled, the over-all monthly data are summarized in Table 1. It can be seen that no distinctive seasonal patterns were clearly evident. There was an indication, however, that the early months of 1952 showed a higher incidence of active strains than the other periods observed. That this high incidence was not due to an unusual number of persons during these months who carried dense populations of active strains is indicated in Figure 4. On this graph each point represents the number of strains of varying activities in the samples of 20 tested from each patient. The samplings from only three months of observation are shown, one of which is January, 1952, the period of high concentrations of these strains. It can be seen that the scattering of the antibiotically active colonies among the patients' samples was broad throughout. It may be pointed out, therefore, that during January, 1952, no tendency was found for a comparatively few patients with dense populations of active strains to weight the data for this month.

One of the important aspects of this study concerned the possible differences in the activity of strains isolated from persons with normal conjunctivae as compared with those from "infected" eyes. Approximately equal numbers of patients in each group were sampled. Thus, 486 patients had inflamed conjunctivae, while 452 were normal in this respect. The remainder had various other superficial infections such as corneal ulcer, hordeolum, dacryocystitis, etc. No significant differences were found in the incidence of antibiotic strains in these groups, either totally or on a monthly basis. The results are illustrated graphically in Figures 5 and 6. It can be readily seen that the fluctuations of prevalence among individual persons and in numbers of strains are similar in the two groups. In these charts, the "infected" group included both the patients with conjunctivitis and those with other infections. Comparison of these subgroups with each other and with

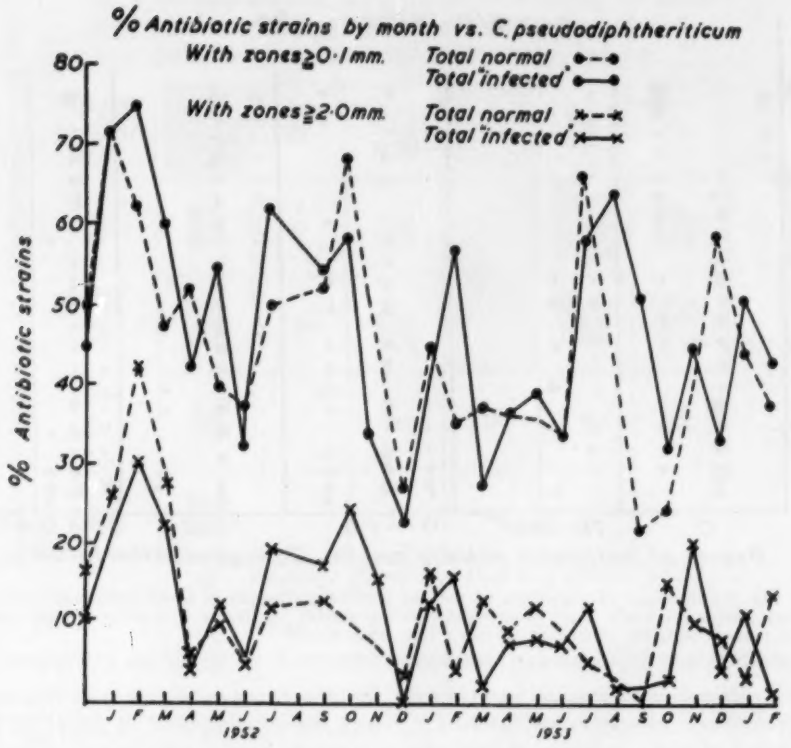

Fig. 5.—Monthly incidence of antibiotic strains from the ocular flora during the period of observation. Each point represents the percentage of the total number of strains examined during the month.

the normals still failed to reveal any significant trends.

Cultures were taken from the nose or skin at the same time as the eye cultures were obtained in 97 persons. Of these, 42 were sampled from all three tissues, while the remainder had only one tissue examined in addition to the eye. It was found that in 26 persons the antibiotic patterns were strikingly different in the various tissues. Examples of some of these are shown in Table 2. The first and third patients represented there had uniform populations of antibiotic-producers in the ocular flora and yet had no active strains in the samples from the nose and only a few in those from the skin. The second patient had all active organisms in the ocular sample, while the strains from the nose and skin were completely inactive. Conversely, Patient 4 showed high concentrations of such antibiotic strains on the skin, but none were found in the eye or nose. Where the populations were similar in the flora of all tissues sampled, all of the strains might be nonactive (as in Patient 9) or all might be highly active (Patient 10). Many of the patients had variable numbers of active strains in each tissue, and often less certain differences seemed to exist in the various samples. Had more complete analysis of the antibiotics been carried out, distinct differences might have been even more frequent. It may be pointed out that a fairly sizable sample of the strains from the various tissues was found by Gram stain to resemble staphylococci. This fact, coupled with the colonial appearance of the colonies selected, makes it appear highly probable

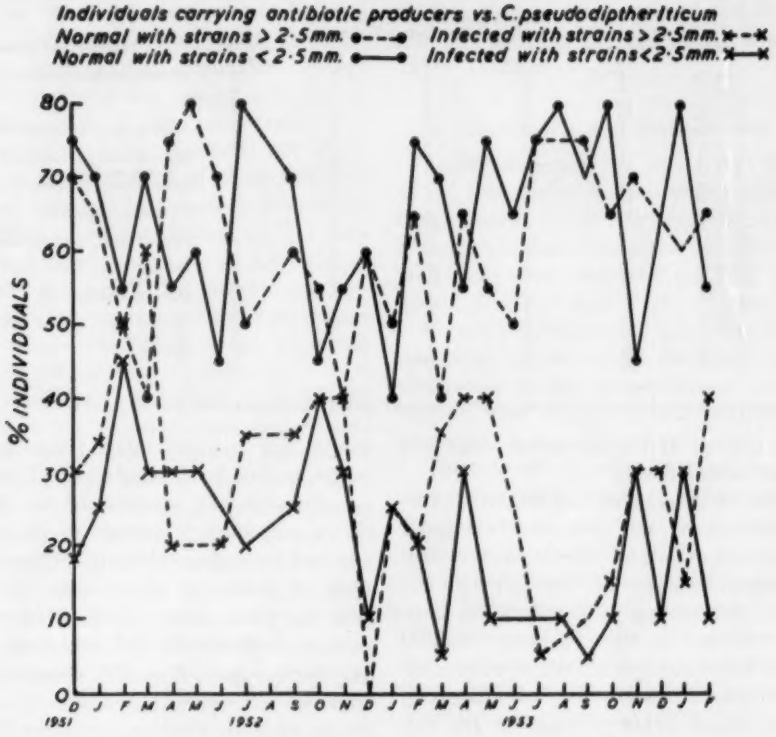

Fig. 6.—Monthly incidence of persons carrying antibiotic strains in any concentration. Each point represents the percentage of patients revealing any active strains among those sampled, during the month.

TABLE 2.—*Antibiotic Activities of Flora of Eye, Nose, and Skin Cultures from the Same Persons*

Patient	Antibiotic Activity Against C. Pseudodiphtheriticum of Strains from		
	Eye*	Nose	Skin (Hand)
1	20 (1.2) 0 (0)	12 (0)	4 (0.6) 6 (0)
2	20 (1.8) 0 (0)	10 (0)	10 (0)
3	15 (1.7) 5 (1.0) 0 (0)	10 (0)	2 (1.6) 8 (0)
4	20 (0)	20 (0)	7 (1.7) 2 (0)
5	11 (1.0) 9 (0)	7 (4.0) 1 (1.5) 3 (0)	10 (0)
6	20 (4.5) 0 (0)	10 (0)	----
7	20 (0)	10 (1.3) 1 (0)	----
8	12 (1.3) 8 (0)	----	15 (0)
9	20 (0)	10 (0)	10 (0)
10	20 (6.0)	10 (6.0)	11 (5.5)

* The first figure represents the number of colonies, while the figure in parentheses represents the zone of inhibition in millimeters.

TABLE 3.—*Follow-Up Cultures from Individual Patients*

Patient	Date	Antibiotic Activity of Sample Strains Against C. Pseudodiphtheriticum					Diagnosis and Remarks
		0	0.1-1.0	1.1-2.0	2.1-4.0	4.1+	
	1/18/52	4*	0	1	15	0	Chronic blepharoconjunctivitis
	2/21/52	5	12	0	3	0	
1	3/10/52	10	0	0	11	0	
	5/11/52	20	0	0	0	0	
2	1/ 8/52	5	0	10	0	1	Normal conj.; local oxytetracycline
	1/ 9/52	0	0	5	0	15	
3	1/24/53	7	0	0	13	0	Normal conj.; preop. local oxytetracycline on 1/24
	2/ 3/53	20	0	0	0	0	
4	11/21/52	7	0	8	0	7	Normal conj.; local oxytetracycline
	1/25/53	17	0	4	0	0	
5	1/21/54	20	0	0	0	0	Chronic conjunctivitis
	2/23/54	0	0	20	0	0	
6	12/16/53	0	20	0	0	0	Normal conj.; local oxytetracycline
	12/18/53	1	19	0	0	0	
7	12/18/53	0	0	20	0	0	Normal conj.; preop. local oxytetracycline
	12/30/53	0	0	20	0	0	
8	3/ 8/53	18	0	2	0	0	Chronic conjunctivitis
	3/17/53	15	0	5	0	0	
9	1/16/52	5	0	0	15	0	Normal conj.; perop. local oxytetracycline on 1/16
	1/17/52	9	0	0	11	0	
10	12/ 3/53	20	0	0	0	0	Normal conj.
	2/25/54	20	0	0	0	0	

* Each figure represents the number of strains of a given activity found in the samples taken from the patient.

that almost all of the organisms examined belonged to this family.

A total of 75 patients had ocular cultures taken on two or more occasions. Of these, 46 were reexamined at intervals of less than one month, usually at one- to two-day periods. Resampling of the flora for antibiotic activities in these persons revealed that significant changes did not seem to occur in 49 of them. Twenty-four of this group had the repeat cultures made on the day following the one on which the original specimens were taken, however. Significant changes in the antibiotic activities of the flora occurred in 20 patients, while 6 showed questionable alterations. In those where changes in the pattern seemed definite, only three were reexamined at a one-day interval. Some of the results on follow-up cultures are shown in Table 3. Thus, in Patient 5 the first culture revealed no antibiotic strains, while the second culture, taken one month later, showed a uniformly active population. Most of the patients examined showed little change, and these are exemplified in the last five subjects shown in Table 3. It may be seen that this could represent the maintenance of an active flora, as well as an inactive one. It is probable here, too, that more precise analysis of the antibiotics involved would reveal more fluctuations than were seen. It is also probable that more extensive data over longer periods of time would also indicate more frequent shifts in the ocular flora population. These data are unfortunately complicated by the fact that a very high percentage of the patients received local chemotherapy during the periods of follow-up observation. However, just as many whose flora remained unchanged antibiotically had local treatment as did those whose flora did change in this respect.

Comment

The results obtained here clearly demonstrate that antibiotic properties of organisms of the ocular flora are abundantly frequent enough to play significant roles in the ecology of these bacterial populations. It is most surprising, in fact, to note that such activities may be present at times in sample colonies from practically all persons tested and may constitute roughly two-thirds of the strains during periods of high incidence. That these inhibitions actually represent antibiotic production is clearly shown by the ease with which active crude filtrates may be produced. In view of this exceedingly frequent occurrence of the strains, and the high degree of in vivo effectiveness of small doses of at least one of these antibiotics,[13] the ecological significance of these properties becomes probable.

The data suggest that there may be significant fluctuations in the prevalence of such strains at times, but the reasons for this are not obvious. More stringent sampling methods from stable population groups would be required for precise information along these lines. It does seem certain that the presence of conjunctivitis is not correlated with the frequency of these antibiotic activities, nor does this seem to be true for other types of ocular infection. Not only were the over-all incidences of such strains essentially the same in the infected and normal groups, but the fluctuations of prevalence of these organisms from month to month were also not significantly different.

The comparative observations made with the flora of the eye, nose, and skin (hand) make it clear that the antibiotic patterns of the clumped Gram-positive cocci in the various tissues may be completely different in many instances. When detailed analysis of the antibiotic agents in sample strains can be more readily carried out, the distinctiveness of the antibiotic patterns in the flora of the various tissues may prove to be even more frequent. These findings add to the reports of others concerning the presence of such organisms in the microflora of the nose and skin.[14,18-20]

The data presented here also demonstrate that the ocular flora can change significantly with respect to these activities in fairly short periods of time. These data are complicated by the use of local chemotherapy during the observation periods, but both persons with and those without significant changes in the flora had similar treatment. At any rate, similar findings have been made in the intestinal flora in the absence of chemotherapy.[31] Both sets of observations indicate the dynamic nature of the bacterial flora equilibrium and suggest that temporal shifts in the antibiotic patterns could easily occur rapidly enough to play roles in resistance mechanisms.

The findings concerning the lack of correlation of the inhibitory activity against the staphylococcal and corynebacterial indicators again point to the multiplicity of the antibiotics involved. It seems likely that a very large number of such substances are secreted by these micro-organisms and that the productive potency of individual strains is rather variable.

Summary and Conclusions

Antibiotic production was found in 47% of 24,389 ocular strains tested against a highly sensitive indicator organism, Corynebacterium pseudodiphtheriticum. These ocular strains were obtained from 1092 persons over a period of more than two years.

Cultures from patients with conjunctivitis and other infections did not show any real differences in the proportion of antibiotic strains when compared with cultures from persons with normal conjunctivae.

The antibiotic patterns of the ocular, nasal, and skin (hand) flora were compared in a small group of patients. In a number of instances the behavior of the strains from the various tissues was completely different.

In follow-up cultures obtained from another group of patients, definite changes in the antibiotic patterns of the ocular flora were found in several within a period of several days to several weeks.

There were monthly fluctuations in the incidence and prevalence of active strains in the persons examined. Although one period of very high incidence of these inhibitory properties was observed, the statistical significance of this finding was not clear.

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Preganglionic Cervical Sympathectomy and Aqueous Flow

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The effect of extirpation of the superior cervical sympathetic ganglion on the aqueous humor dynamics in rabbits was reported in a previous paper.[6] One day following this operation a marked decrease of the intraocular pressure and of the rate of aqueous flow was found, but a few days later the values were restored to normal.

Preliminary results of a similar study concerning the effect of preganglionic cervical sympathectomy on the aqueous humor dynamics were reported in the same paper. The purpose of the present work was to complete and report this investigation. After the preganglionic cervical sympathectomy one day was allowed to elapse before the measurements were made in order to establish a postoperative steady state.

Material and Methods

Male pigmented rabbits weighing 2 to 2.5 kg. were used. The preganglionic cervical sympathetic nerve fibers were divided on the right side, with use of general anesthesia (pentobarbital sodium 65 mg/ml., 0.5 ml/kg. body weight). The intraocular pressure was measured by means of an electronic tonometer (V Mueller) and Grant's method of tonography[4] was used according to the method of Kornbluth and Linnér.[5] Throughout the study the right eye was studied before the left. The calibration tables of Friedenwald (1954)[2] were used for the calculations of the results.

Received for publication Jan. 26, 1957.

This study was supported in part by a grant from the Kellogg Foundation and in part by a training grant from the National Institute of Neurological Diseases and Blindness.

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Results

Table 1 demonstrates the measurements of the intraocular pressure without tonography which can influence the result of the second eye. No significant difference between the operated on and the intact side was found.

TABLE 1.—*Intraocular Pressure Following Preganglionic Cervical Sympathectomy, Right Side* *

Time, Days			Right Eye	Left Eye	R/L
1		m	22.7	24.3	0.95
	P_o	e	1.39	1.59	0.058
		n	9	9	9
4		m	21.7	22.4	0.99
	P_o	e	1.32	1.56	0.070
		n	9	9	9

* P_o, intraocular pressure in mm. Hg; m, arithmetic mean; e, standard error of the mean; n, number of experiments.

Table 2 shows the results obtained by tonography. The value of the intraocular pressure was taken from the beginning of the tonographic tracing. There was a slightly higher pressure in the right eye,

TABLE 2.—*Tonographic Measurements Following Preganglionic Cervical Sympathectomy, Right Side* *

Time, Days			Right Eye	Left Eye	R/L
1		m	18.1	17.1	1.08
	P_o	e	1.31	1.06	0.054
		n	15	15	15
		m	0.26	0.24	1.08
	C	e	0.013	0.012	0.085
		n	15	15	15
	F	m	2.37	1.94	1.22
4-6		m	18.8	18.1	1.10
	P_o	e	1.23	1.51	0.090
		n	14	14	14
		m	0.25	0.27	0.93
	C	e	0.018	0.015	0.056
		n	14	14	14
	F	m	2.45	2.46	1.00

*P_o, intraocular pressure in mm. Hg; C, coefficient of facility of outflow, cu. mm/minute/mm. Hg; F, rate of aqueous flow, cu. mm/minute, calculated from the mean values for P_o and C; m, arithmetic mean; e, standard error of the mean; n, number of experiments.

where tonography was performed first, although the difference was not statistically significant. The coefficient of facility of outflow did not show any significant difference between the operated on and the intact side.

Comment

No significant change of the intraocular pressure or of the coefficient of facility of outflow was found after preganglionic cervical sympathectomy.

Assuming that the episcleral venous pressure remained constant, no significant change in the rate of aqueous flow was found. Such an assumption could be considered valid according to the studies by Kornbluth and Linnér [5] and by Linnér and Prijot [6] showing that the stability of the episcleral venous pressure was not disturbed by procedures such as carotid ligation and cervical sympathetic ganglionectomy.

The contrast between the marked suppression of aqueous flow following removal of the superior cervical sympathetic ganglion and the undisturbed aqueous flow following preganglionic sympathectomy is striking. Friedenwald and Buschke [3] showed that adrenalectomy inhibited certain aspects of the intraocular secretory mechanism, but they did not reveal any effect of preganglionic cervical sympathectomy on the secretory mechanism.

The lower value of the rate of aqueous flow found in the left eye which could have been influenced by tonography performed on the right eye is in agreement with the decrease of the aqueous flow in the second eye found after tonography on the first eye in normal rabbits [5] and the more marked decrease found after compression with 40 gm. on the first eye.[7]

The values of the intraocular pressure, facility of outflow, and rate of aqueous flow are in good agreement with the results found in previous experiments under the same general anesthesia.[5,8]

In a previous study Becker and Linnér [1] found that the ascorbic acid concentration in the aqueous humor of the anterior chamber increased on the side of preganglionic sympathectomy at plasma ascorbic acid levels below saturation. Above saturation level no such increase on the operated on side was found.

The fact that no significant change in the rate of aqueous flow could be revealed by the tonographic measurements supports the assumption that the effect of preganglionic cervical sympathectomy on the ciliary processes is limited to vasodilatation.

Summary

The effect of preganglionic cervical sympathectomy on the aqueous humor dynamics was studied in rabbits. No significant change was found in the intraocular pressure, in the facility of outflow, or in the rate of aqueous flow.

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The Modern Treatment of Uveitis

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The diagnosis and modern treatment of uveitis are not simple matters, because, as all know who have seen and handled such cases, uveitis is one of the most difficult problems faced by ophthalmologists. However, the progress that has been made toward a more satisfactory rate of diagnosis has resulted in an increased efficacy of modern modes of treatment.

The key to rational and successful treatment lies in accurate diagnosis. The cause in most cases of uveitis has been obscure, and adequate criteria have not been brought forth to crystallize diagnosis, thus creating a great deal of pessimism. This attitude has reached such proportions that it is sometimes said that a cause is found in only 5% to 10% of cases of uveitis; the other 90% to 95% of cases remain unclassified, and, therefore, treatment must be empirical. In the light of recent discoveries and the crystallization of more accurate criteria, this pessimism appears to be unwarranted, for a larger percentage of cases now can be classified. Study of Woods'[1] work reveals that, as knowledge and understanding of this group of diseases have increased, his criteria for specific diagnosis have become more exacting and rigid. Thus, he attributed the cause of uveitis to tuberculosis in 79% of cases in 1941, in 52% in 1944, and in only 23% in 1953. While the frequency with which uveitis has been attributed to tuberculosis has decreased with added knowledge, the recognition of diverse other causes has been increasing and the number of cases considered to be of unknown cause has been steadily decreasing. In Woods'[1] latest reported series, of 191 cases, published in 1953, he considered only 18% to be of unknown etiology, while making a positive or presumptive diagnosis in the remaining 82%. These figures agree with those published recently by other authors. Thus, Berens and Bickerton[2] relegated only 25% of cases, Vesterdal[3] only 24%, Alvaro[4] only 19%, and Bennett[5] 37% to the group of unknown etiology. Also, the figures of Woods pertaining to the cause of nongranulomatous uveitis agree closely with the work of Leopold and Dickinson,[6] who used entirely different methods to arrive at their conclusions.

It is also important to determine, if possible, whether uveitis is granulomatous or nongranulomatous before further diagnostic work is begun, because this distinction may be an important factor in determining what form the diagnostic survey may take. When the clinical picture is clearly that of granulomatous uveitis, it is permissible to omit the examinations for a nongranulomatous type of uveitis, such as studies of bacterial hypersensitivity. Conversely, only in the rare cases of nongranulomatous uveitis that obviously are allied to focal or acute diseases should the routine examination for evidences of granulomatous disease be left undone. It is beyond the scope of the present discussion to take up the criteria distinguishing the granulomatous from the nongranulomatous type, but the differences are rather definite. Whether the uveitis is anterior or posterior offers no clue to the differentiation; it is not true that posterior uveitis is synonymous with a granulomatous infection and vice versa. Usually the differentiation is easy, but admittedly there are cases that show

Received for publication Jan. 15, 1957.

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characteristics of both types. When the least doubt exists concerning classification or when evidence is present of both granulomatous disease and a nongranulomatous reaction, a complete diagnostic survey should be made. This differentiation of uveitis into these two broad clinical groups has definite import on the choice of treatment.

It is also important that the ophthalmologist be responsible for the diagnostic survey in uveitis. In many instances, perhaps in the majority, the ophthalmologist sees a patient with uveitis, realizes a diagnostic survey is indicated, and sends the patient to an internist, placing the responsibility for diagnosis on the internist. The ophthalmologist should captain the diagnostic team, for only he is acquainted with the enormous complexity of the problem and the many and varied etiologic factors that may be responsible. If the percentage of unclassified cases is to be reduced, the ophthalmologist must not rely solely on the results of routine physical examination and the usual laboratory studies. As emphasized by Woods, it is the duty of the ophthalmologist to channel the investigations into the necessary specific fields, to order all pertinent examinations, to bring together various specialists whose special examinations may help determine the cause, to command the various laboratory and immunologic studies, and, finally, to analyze the results of the survey as a whole and, with his special knowledge of the ocular picture, make a positive or tentative etiologic classification, if such is possible.

Specific Treatment

Specific treatment is directed at the actual cause of the ocular disease. In granulomatous uveitis, specific therapy is designed either to destroy the causative agent or to inhibit and restrain its growth. In nongranulomatous uveitis, specific therapy accomplishes removal of the underlying factor responsible for uveal inflammation.

Syphilis.—The treatment of syphilitic uveitis presents two problems, namely, the healing of the immediate lesion and the treatment of the generalized infection. At present, administration of penicillin has replaced almost completely the use of metal chemotherapy in the treatment of syphilis. Prompt healing of early syphilitic uveitis may be expected within a few days with appropriate penicillin therapy.[7] Either a local or a systemic Herxheimer reaction will develop in at least half the patients so treated; however, neither is sufficient to cause alarm or interruption of treatment. The local response in uveitis consists of temporary intensification of the inflammatory reaction, with increased clouding of the aqueous, appearing 8 to 16 hours after the first injection of penicillin and subsiding within 12 additional hours.

Penicillin may be given under ambulatory conditions. It may be given in individual intramuscular injections of 600,000 units for 10 treatments, a total of 6,000,000 units. These injections may be given daily or every third day. This regimen may be expected to produce failures in 10% to 15% of patients so treated within the first 12 to 18 months of their infection. After completion of therapy, the patient must be closely followed clinically, with monthly serologic tests for the first year. In cases of early syphilis, routine examination of the cerebrospinal fluid should be done about the sixth month. If the patient remains clinically and serologically negative, observations within the second year may be spaced to every three months, and in the third and subsequent years to every six months. If clinical or serologic relapses occur, treatment with penicillin again is instituted, the results of retreatment being as good as those of the original course. Because of the superiority of penicillin in the treatment of syphilis, other antibiotics should not be used except for patients completely intolerant of penicillin.

Tuberculosis.—Specific therapy is directed toward enhancement of specific resistance to the infection, to reversal or diminution of the tissue hypersensitivity that is responsible

for the destructive inflammatory phase of the tuberculous lesion, and to a direct attack on the tubercle bacilli, leading to their destruction or to inhibition of their proliferation. Enhancement of specific resistance is accomplished by employing the usual nonspecific procedures, such as rest, relief of tension, an adequate diet, and removal of debilitating infections. Formerly, one of the most important therapeutic problems in ocular tuberculosis was to remove the hypersensitivity that resulted from the infection, restoring the ocular tissues to their primary nonreactive status. This was accomplished by desensitizing the tissues to tuberculoprotein. With the introduction of chemotherapy and antibiotic therapy for tuberculosis, desensitization by use of tuberculin has lost some of its importance. Much time was needed to desensitize patients to tuberculoprotein. Because disastrous focal reactions in the eye occasionally followed treatment with tuberculin and because of the long time necessary for such treatment, it is rarely used now.

The sulfones were the first chemotherapeutic agents used against tuberculosis. They were not particularly satisfactory, since their action appeared to be chiefly bacteriostatic. More chemical agents gradually became available for the treatment of tuberculosis, including aminosalicylic acid, U. S. P. isoniazid (isonicotinic acid hydrazide), and streptomycin. The drawback of these agents was either their high failure rate or the rapid development of resistant organisms. However, when various drugs were combined they proved to be synergistic and favorable results became much commoner.

The regimen now recommended includes administration of equal parts of streptomycin and dihydrostreptomycin, 1 gm. given intramuscularly every other day, aminosalicylic acid U. S. P. (12 gm. per day) in doses of 3 gm. every six hours around the clock, and 300 mg. of isoniazid given daily in divided doses every eight hours. Treatment should be continued for a minimum of 21 days, regardless of the therapeutic response. If a favorable change is absent at this time, the validity of the diagnosis should be questioned and the situation should be reevaluated. If a favorable response is observed, treatment must be continued for a minimum of four months to obtain a cure.[8] Such treatment is so specific that Leopold[9] suggested using it as a therapeutic test to confirm a diagnosis of ocular tuberculosis. If no response occurs, this may be evidence against tuberculosis as a cause. Leopold[9] considered that all these drugs should be used in combination, so that the development of resistant organisms will be greatly lessened.

One of the most recent trends is the use of steroids along with antituberculotic drugs in the treatment of ocular tuberculosis. Steroids given alone may cause exacerbation of tuberculous uveitis. However, Leopold[10] has shown that steroids apparently do not reduce the effectiveness of antibiotics against susceptible organisms. He considered that steroids might prove useful as adjuncts in the treatment of uveitis caused by infections such as tuberculosis because they reduce the severity of the inflammatory reaction while the antibiotic overcomes the growth and multiplication of the infecting agent. By reducing the inflammatory reaction, the steroids may reduce some of the destruction of tissue and subsequent visual loss. Kratka[8] stated that, despite reports contraindicating the use of steroids in tuberculosis, he employed cortisone in addition to isoniazid and streptomycin and obtained good results. He also considered that the steroids, by inhibiting the tuberculous inflammatory reaction, allowed isoniazid and streptomycin to attack the tubercle bacilli more rapidly. According to Lepri,[11] cortisone may be used with care in granulomatous ocular tuberculosis if combined with appropriate antituberculotic antibiotics or chemotherapeutic agents. Gordon[12] also did not consider that systemic steroid therapy is contraindicated in ocular tuberculosis. He thinks that true intraocular tuberculous infections are rare and that such a diagnosis

is always open to question. However, if the ophthalmologist thinks he is dealing with tuberculosis, Gordon stated, systemic steroids should be employed in addition to such antituberculotic agents as aminosalicylic acid, U. S. P. isoniazid, and streptomycin.

Brucellosis.—As was the case in tuberculosis, early therapeutic efforts in brucellosis largely centered on attempts to stimulate resistance or acquired immunity in the patient by the use of repeated injections of brucellin. The results were not satisfactory, and so this form of treatment was abandoned. The most successful vaccine thus far prepared for the treatment of chronic brucellosis appears to be the oxidized vaccine of Foshay. Administration of this vaccine over a prolonged period has given remarkably good results in the recurrent iritis and scleritis associated with chronic brucellosis, but it is not clear whether the benefits observed after a prolonged course of Foshay's vaccine are the result of desensitization or of stimulation of artificial immunity. It is difficult, if not impossible, to produce any lasting immunity with this vaccine.

Since the introduction of antibiotics, the treatment of choice for ocular brucellosis is chlortetracycline (Aureomycin), 750 mg. four times a day, combined with dihydrostreptomycin, 1 gm. per day, continued for four to six weeks. Woods [1] advocated use of chlortetracycline alone for 10 to 14 days, followed by intramuscular injections of Foshay's vaccine every second day, beginning with 0.1 ml. of the T-1 concentration and continuing until a dose of 0.5 ml. of the T-500 concentration is reached. Most observers consider that combined chlortetracycline-dihydrostreptomycin treatment offers the best chance of success.

Toxoplasmosis.—Beverley and associates [13] reported good results in experimental ocular infection employing diaminodiphenylsulfone and suggested that it may be useful in human infection. Eyles and Coleman,[14] after investigating the antitoxoplasmic activity of many antibiotics, reported in 1952 that pyrimethamine (Daraprim) was singularly effective against the protozoon causing toxoplasmosis. In 1953, these same investigators [15] reported that a combination of sulfadiazine and pyrimethamine was more than six times as active as would be expected from their additive action alone. Various doses have been employed. Hogan [16] gave 25 mg. of pyrimethamine three times a day combined with 4 gm. of sulfadiazine daily, continuing the treatment for two to three weeks. Burnham and Beuerman [17] used various doses and continued treatment for as long as 10 months. Woods [1] advocated a smaller dose, consisting of 25 mg. of pyrimethamine daily for three weeks and then 25 mg. every other day for an additional three weeks. During this time, sulfadiazine is given concomitantly in divided doses, with a total of 3 gm. each day. Frenkel,[18] discussing the paper of Ryan and co-workers, suggested that cortisone, which sometimes makes chorioretinitis in toxoplasmosis worse when used alone, theoretically should minimize the inflammatory reaction produced by rupture of pseudocysts in the eyes of patients being treated with pyrimethamine and sulfadiazine. Beverley and associates [13] suggested that, in addition to chemotherapeutic inactivation of the parasite, allergy to the organism also should be treated, preferably with one of the corticosteroids.

Pyrimethamine is toxic and may produce a megaloblastic change in the erythrocytic precursors in bone marrow and inhibition of leukopoiesis, causing anemia and leukopenia. Gastrointestinal and cutaneous side-effects also are common. The rash responds promptly to antihistaminics, and in no cases does depression of the bone marrow fail to recover rapidly after cessation of therapy or reduction of the dose of pyrimethamine to 25 mg. per day. Nevertheless, pyrimethamine and sulfadiazine in the treatment of human disease must be used with caution. At a conference on granulomatous uveitis at the National Institutes of Health in 1954, Feldman [19] stated that the combination of pyrimethamine and sulfadiazine might cause remission in any patient with infectious

uveitis. Therefore, a therapeutic response is not necessarily an indicator of a specific effect against Toxoplasma. Leopold [10] pointed out that the experimental work with these agents has dealt with acute infection. In all probability, the agents are able to work best on actively growing protozoa, and it is questionable whether they will be effective against chronic infection, in which the organisms are multiplying slowly, if at all. Nevertheless, it is encouraging to realize that compounds are available which may be helpful against toxoplasmosis.

Trypanosomiasis.— In Africa, ocular trypanosomiasis with uveitis is frequent. The infection reacts favorably to the intravenous administration of arsenicals, such as sodium arsanilate (Atoxyl) or arsphenamine, given in conventional doses.

Actinomycosis.—Penicillin is the antibiotic of choice in the treatment of this fungous disease. A dose of 600,000 units a day is recommended for a 10-day period, possibly with use of potassium iodide as an adjuvant treatment. As yet there are no reports of a successfully treated proved case of uveitis caused by actinomycosis.

Blastomycosis, Cryptococcosis, and Histoplasmosis.—Uveitis reported to be caused by these fungous diseases has not healed spontaneously but the disease has progressed and the eyes have been lost. However, several new agents may prove to be of value. Nystatin may be given orally in a dose of 1,500,000 units per day. It is almost nontoxic and has been used a great deal in gastrointestinal infections caused by fungi. The most promising drug yet used in the treatment of these three fungous diseases is ethyl vanillate. Minimal levels of 20 mg. per 100 ml. of blood are necessary to produce any therapeutic effect. To maintain this level, daily oral administration of 45 gm. usually is required. The usual regimen is to begin with a dose of 15 to 30 gm. per day and slowly increase it to 45 gm., which is maintained for six or seven weeks to obtain a full therapeutic effect. The drug is potentially toxic but does not regularly produce toxic reactions, and these are reversible if detected early. These drugs are unproved in uveitis; however, in view of the gloomy prognosis for intraocular fungous infection, they might be worthy of trial.

Onchocerciasis.—Although not seen in the United States, this is one of the commonest causes of uveitis in some parts of the world. Treatment was discouraging until recently, but two drugs are used now. The drug of choice appears to be suramin sodium (Antrypol), given in a dose of 1 gm. once weekly for six or seven weeks. Toxic reactions may develop but are not serious. The second drug, which is of value principally after a course of suramin sodium has failed, is diethylcarbamazine citrate (Hetrazan), given in a dose of 35 to 140 mg. three times a day for three weeks. Initial use of these two drugs in uveitis caused by onchocerciasis is encouraging.

Nonspecific Therapy

Since specific treatment is not available in the many cases of uveitis in which the cause is unknown, nonspecific therapy is still important. Woods [1] divided nonspecific therapeutic procedures into five general groups.

General Measures.—This group includes those general hygienic procedures designed to improve the general health of the patient and to increase resistance to a disease process. Little need be said about these measures, since they are common to the treatment of any infectious disease anywhere in the body. They include rest, proper diet, fresh air, proper exercise, regular elimination, and removal of debilitating foci of infection. Berens [20] said it is important to do everything possible to increase nonspecific resistance. He stated that this should be done with mental and physical rest, sunshine, fresh air, proper diet, and administration of supplemental vitamins, particularly in older patients and in those whose dietary habits are improper. Therefore, in the treatment of any form of uveitis, it is the duty of the ophthalmologist to inquire into the personal life and hygiene of the patient and to advise

all reasonable measures to improve and correct these factors.

Local Measures.—This group includes all local procedures that are designed to ameliorate the inflammation, limit the spread of the infection, prevent ocular complications, and make the patient more comfortable.

The first consideration in this group is the use of mydriatics, which is the first step in the treatment of all forms of anterior uveitis. Gordon [12] stated that mydriatics are not necessary when systemic steroid therapy is employed in the treatment of anterior uveitis unless adhesions are present or forming. Rather than risk complications, it appears safer to employ mydriatics routinely in all cases of anterior uveitis. However, there is no indication for their use or proof that they are of benefit in posterior uveitis. The usual mydriatics are also cycloplegics and relax or paralyze the ciliary muscle. Mydriatics benefit patients who have anterior uveitis by a fourfold effect. First, by relaxing the ciliary muscle they relieve pressure on the ciliary arteries and theoretically increase the flow of blood to the iris. Secondly, by dilating the pupil they tend to prevent the formation of posterior synechiae or break any posterior synechiae already formed, enlarge the pupillary space, and increase the communication between the anterior and posterior chambers. Thirdly, cycloplegic action puts the eye at rest by releasing spasm of the pupilloconstrictor and ciliary muscles. Finally, as Adler [21] pointed out, mydriatics decrease the permeability of the blood vessels to protein, resulting in reduced exudation.

The mydriatic of choice is atropine, because of its powerful and long action. It is usually employed in the form of drops of a 1% solution or as an ointment instilled once or twice daily. Should the patient have or acquire sensitivity to atropine, scopolamine or, more recently, oxyphenonium bromide (Antrenyl) may be substituted. Scopolamine may be used in a 0.5% solution; the duration of its effect is shorter than is that of atropine. Oxyphenonium bromide is a new anticholinergic and autonomic ganglion blocking agent that may be used in a 5% solution; the mydriasis so produced is more rapid and more nearly complete and the duration of cycloplegia is longer than with use of a 1% solution of atropine.[22] In fact, the cycloplegia and mydriasis produced by 5% oxyphenonium bromide are so intense that they cannot be counteracted with use of 2% pilocarpine nitrate, 0.5% physostigmine (eserine) salicylate U. S. P., 1.5% carbachol (Carcholin), or 0.1% isoflurophate (DFP), or by the cumulative action of all these agents together. Therefore, it should be used only when there is no danger of precipitating glaucoma.

If any increase in ocular tension is present, a less-powerful and shorter-acting mydriatic should be used, such as 2% homatropine hydrobromide U. S. P. or 10% phenylephrine (Neo-Synephrine) hydrochloride. The most recent and probably the best of the shorter-acting mydriatics is 1% cyclopentolate (Cyclogyl) hydrochloride. This drug produces better mydriasis and cycloplegia than does homatropine,[23] and yet it has a shorter duration of action and is counteracted effectively and rapidly with 2% pilocarpine. If synechiae already have formed and an extremely powerful mydriatic is desired, the Mydricain mixture advocated by Duke-Elder may be employed; this is a mixture of atropine, cocaine, and epinephrine. Another powerful and short-acting mydriatic mixture is a combination of phenylephrine, homatropine, and procaine. These mixtures are used as subconjunctival injections.

The next local measure of importance is the use of heat, which is employed in uveitis with the object of producing local vasodilatation and hyperemia of the tissues. Hyperemia supposedly facilitates absorption of inflammatory products and possibly promotes local concentration of circulating antibodies in the inflamed uvea. The actual therapeutic value of local heat is the subject of some controversy and difference of opinion, and

its use as a therapeutic measure is on the wane. The actual increase in temperature produced in different parts of the eye by various means has been determined by a number of investigators. The figures given by Moncreiff and associates [24] are as good as any. Moist heat applied directly to the closed lids by compresses and dry heat by a hot box or an electric pad were given at a maximum of about 127 F for 15 to 20 minutes, the limit tolerated by the skin. This increased the temperature at the conjunctival level by 3 to 4 degrees F and that in the anterior chamber by 2 to 4 degrees F; a negligible increase was noted in the posterior and vitreous chambers. An infrared lamp used for 15 to 20 minutes at just below the erythema dose increased the temperature in the anterior ocular segment by about 5 degrees F and that in the posterior segment by about 2 degrees F. Diathermy may be given by the conventional method or in the form of high-frequency waves. There appears to be little choice between these two methods. Both are efficacious in that they produce an increase of 4 to 5 degrees F in the temperature of the deep tissues. In actual practice, moist applications, the hot box, or the electric pad is used in the treatment of iritis or iridocyclitis for 15 to 20 minutes three to four times per day. The infrared lamp is used for a similar period, but usually not more than once or, occasionally, twice daily. Diathermy is used for a longer period, up to three or four hours, but is given usually once every three or four days. Apart from its soothing analgesic action, it is doubtful whether heat has much therapeutic value.

Another local procedure that can be used in the treatment of uveitis is paracentesis. Puncture of the anterior chamber and drainage of the aqueous is employed in uveitis to give temporary relief from increased ocular tension or to control acute exacerbations of inflammation or for both purposes. Since the aqueous is quickly regenerated, paracentesis will decrease ocular tension for only a brief period, rarely more than 18 to 24 hours. When employed to give temporary relief from increased tension caused by acute inflammation, a better regimen is the use of acetazoleamide (Diamox) to cut down the inflow of aqueous and some procedure, such as steroid therapy, to control the inflammation. Drainage of the aqueous during acute exacerbation of uveal inflammation sometimes is followed by pronounced diminution of the inflammatory reaction. This improvement possibly may result from removal of hypothetic toxins in the primary aqueous, but more probably it is due to an increase in antibodies in the secondary aqueous. After paracentesis and drainage of the primary aqueous, antibodies are present in the re-formed aqueous in greatly increased amounts, even up to 100 times or more their concentration in the primary aqueous, and the antibody content of the third aqueous approaches that of the blood plasma. Paracentesis is sometimes of value in granulomatous uveitis when the patient is pursuing a downhill course or is undergoing an intractable exacerbation. It is of little or no value in acute nongranulomatous uveitis, in which the inflammation can be controlled better and more safely by steroid therapy.

Irradiation has been used as local treatment in uveitis. The rationale appears to be that such therapy produces prolonged hyperemia of the inflamed tissues and that such hyperemia has a beneficial effect on the disease process. Favorable reports on the use of roentgen rays in the treatment of uveitis have come from Alvaro,[25] Di Marzio and Strazzi,[26] and Fried.[27] However, the extensive use of irradiation in uveitis on the basis of the assumption that the uveal inflammation is related to primary constriction of the arterioles and secondary dilatation of the capillaries is not justified. Also, Pendergrass and Hodes [28] pointed out that inflammation produces so much vascularization and engorgement that added irradiation can do little more. In addition, there is always the danger of possible damage to the crystalline lens, with resultant cataract forma-

tion, in irradiation of the uveal tract. At present, therefore, roentgen therapy is not recommended as a routine nonspecific procedure in the treatment of uveitis. The use of nonpenetrating diathermy coagulation in the treatment of uveitis has been reported,[29] but the results have been unimpressive and this treatment is not recommended.

Nonspecific Drugs and Chemical Compounds.—This group of procedures includes the administration of drugs or chemical compounds that are supposed to have a favorable influence on ocular inflammation. The use of these agents has been entirely empirical, and their mode of action never has been explained satisfactorily.

The most time-honored of these drugs are the salicylates. It has been well known for a long time that many patients who have acute iridocyclitis respond remarkably well to large doses of sodium salicylate. Salicylates were used long before fever therapy was discovered. The dose recommended by Gifford, in 1900, for the control of acute uveal inflammation was 0.065 gm. per pound of body weight per day.[30] As soon as relief was obtained, the daily dose was decreased to a total of 6 gm. and then to 4 gm. The action of the salicylates in uveitis never has been explained. It is a matter of common observation, however, that evidence of ciliary inflammation in acute iritis or iridocyclitis lessens and pain decreases when the patients are given sodium salicylate. When administration of the drug is stopped, the symptoms return. While use of salicylates has declined with the increase of enthusiasm for antibiotics and steroids, it should be remembered that salicylates undoubtedly have a depressant action on uveal inflammation, and there is no contraindication to their use in combination with more modern treatment.

When sulfones and antibiotics first became available, they were used on a basis of trial and error. It soon became evident that both sulfones and wide-spectrum antibiotics had pronounced therapeutic action against the causative agent in a great number of infections for which adequate therapy previously had not existed. It was also apparent, however, that such drugs were of limited usefulness in endogenous uveitis. The sulfones and the sulfonamide drugs have been used extensively in uveitis of unknown cause and have been found almost completely inefficacious. Antibiotics also have been equally ineffective as nonspecific agents. Many ophthalmologists almost routinely treat patients who have uveitis of undetermined cause with penicillin or some other antibiotic. With the exception of uveitis caused by syphilis, tuberculosis, or brucellosis, antibiotic treatment has been without therapeutic effect. If the presence of any of these three diseases is suspected, the patient should, of course, be given a trial of the indicated antibiotic. However, in the present state of knowledge, little indication exists for the use of sulfones, sulfonamide drugs, or antibiotics as nonspecific agents in endogenous uveitis.

Mechlorethamine (nitrogen mustard) has been recommended[31] recently for the treatment of severe and intractable uveitis of unknown cause, and startlingly good results have been reported in some of the patients so treated. The action of mechlorethamine in uveitis is believed to be nonspecific, inhibiting in some way the development of the inflammatory cycle. The drug probably does not have any specific action on the exciting agent. The usual dose is 5 mg. given every four to six days until a total of 25 mg. is given. The blood and urine must be observed carefully for untoward effects. Until more information is available, it is impossible to assess the value of this agent.

Intravenous injections of solutions of copper lactate have been used by some workers as nonspecific therapy in iridocyclitis.[32] It was found particularly effective in iridocyclitis that probably was caused by a virus and was resistant to other forms of treatment. A dose of 5 to 10 ml. of a 1% solution is used daily, and 3 to 12 injections suffice for a cure. The number of cases

reported, however, is too meager to allow any definite conclusions to be drawn.

Another agent recently used parenterally to treat uveitis is trypsin.[33] It is claimed to be a nonspecific anti-inflammatory enzymatic agent with systemic action. Trypsin in oil is injected deep into the gluteal muscle, and the initial dose is 0.5 ml. one to three times daily until clinical improvement is achieved. Then the dose is reduced gradually. Leopold[34] was unimpressed with the use of enzymes such as trypsin in patients who had choroiditis and uveitis. Clinical evaluation of such an agent is difficult. Trypsin has been more impressive in the laboratory under ideal experimental conditions than it has been in clinical use. It is not being employed much in the treatment of uveitis at present.

Other than the steroids, the most important nonspecific agent for treating uveitis probably is phenylbutazone. It has an analgesic, antipyretic, and antiphlogistic action resembling that of cortisone, suggesting simple stimulation of the pituitary-adrenal axis. However, phenylbutazone apparently does not affect urinary excretion of ketosteroids, the eosinophil count, or the insulin requirement in diabetes. It is definitely toxic and should be employed only with full awareness of this characteristic. The untoward side-effects include edema, retention of fluids, rashes, leukopenia, thrombocytopenia, and agranulocytosis. Study of 1594 patients receiving phenylbutazone indicated that toxic reactions were sufficiently severe in 12% to make it necessary to discontinue use of the drug.[35] However, the incidence of these toxic effects appears to be diminishing, there being only 3 such instances in 150 cases recently reported by Harris and Klein.[36] Since phenylbutazone acts as a solvent for aminopyrine, European workers mixed these agents together in a 30% concentration, calling the new compound "Irgapyrine." Irgapyrine has been used extensively in Europe in the treatment of uveitis and has been found to have a pronounced anti-inflammatory effect.[37] Studies in the United States have shown that the anti-inflammatory effect is produced entirely by the phenylbutazone in this compound. Irgapyrine is not available in this country, but phenylbutazone is available in 200 mg. tablets for oral use. The oral dose of phenylbutazone is 800 mg. a day given in divided doses every six hours until a therapeutic response is obtained. The dose then is decreased gradually to the lowest level at which a therapeutic response can be maintained. In this dosage, its effect is similar to but less effective than that of the steroids. It is probable that phenylbutazone will have some usefulness in ophthalmology in the diseases and disorders in which steroids are contraindicated. It also appears to be especially effective in postoperative iridocyclitis, acute "rheumatic" iritis, and metaherpetic inflammation. The blood and urine of all patients receiving phenylbutazone must be studied systematically for the early detection of any untoward reaction on the hemopoietic system or the kidneys.

Fever Therapy.—This method of nonspecific treatment was first used in ophthalmology in 1915 by Schmidt, who injected milk to produce fever. Typhoid vaccine was first given intravenously by Kraus and Mazzada, in 1912, and was first used as a nonspecific protein to produce fever several years later, by Miller and Lusk. From 1915 on, the use of fever therapy in ophthalmology became a favored and occasionally an extraordinarily effective manner of treating ocular inflammation. Fever therapy during the past 40 years has been a valuable tool in ophthalmic therapeutics; only recently, with the development of specific forms of therapy and of better nonspecific treatment, has the use of fever therapy declined.

Richet[38] divided fever therapy into passive and active methods. Passive fever is produced by application of energy to the exterior or the interior of the body. External heat may be supplied by hot-water baths, electric blankets, or air-conditioned cabinets. A number of short-wave devices have been described that heat the interior

but not the surface of the body. These are used ordinarily in conjunction with some method for preventing dissipation of heat from the body surface. Proponents of internal methods stress that they are more physiologic than is use of heat cabinets, since the ambient temperature is not increased. Advocates of the Hypertherm cite its safety, although the period of induction of fever is longer than with use of high-frequency electric currents. Passive fever avoids the unpleasant symptoms and the undesirable vasoconstriction that occur during the induction of active fever. The temperature is quickly increased, and the fever may be maintained at any level for any period desired. Usually a greater febrile response is obtained than that which can be produced safely with active fever, but there is greater discomfort during the febrile phase than occurs with active fever. If the beneficial results of fever therapy are directly attributable to the amount and duration of fever, then passive fever would be the more desirable method of treatment.

Active fever is produced by systemic infections and by the injection of various bacterial products and foreign proteins. The increased temperature in active fever is the result of increased production of heat combined with decreased dissipation of heat. Of these two factors, the decrease in loss of heat appears to be by far the more important.[39] Seibert[40] demonstrated that the induction of fever by injection of foreign protein, no matter what the agent used, is due to a common pyrogenic factor, apparently a polysaccharide, that is heat-stable and passes bacterial filters. Thus, the term "foreign-protein therapy" appears to be inaccurate, since it is actually a polysaccharide that is involved. Reactions to protein are not characterized by fever but by an anaphylactic type of response.[41] However, the term foreign-protein therapy has become so widely used in the literature that it will continue to be used in this paper.

The mechanism whereby pyrogenic agents beneficially affect ocular diseases never has been clarified. It has been stated that the injection of foreign proteins excites the immunologic mechanism of the organism to renewed activity. Hektoen, in 1917, remarked that the use of antigenic materials could excite the elaboration, in high titers, of antibodies against antigens to which the organism previously had been rendered sensitive. This so-called anamnestic response also has been recorded by Selye[42] as part of the response of the organism to stress. Ashton[43] referred to this recently when he talked about the "nonspecific stimulation of antibodies," meaning that a nonspecific stimulus may result in the mobilization of preformed antibodies. With the introduction of the "alarm reaction" and "adaptation syndrome" by Selye, in 1946, the concept began to emerge that the pyrogenic agents owe their effectivity to production of an alarm reaction in the body. The beneficial effect then would be expected to occur in the countershock phase, when an increase in resistance takes place.

Sayers and Sayers[44] demonstrated that killed typhoid organisms produce histologic changes in the adrenal cortex of animals characteristic of the general response to stress. Altschule and associates[45] studied eosinophil counts, lymphocyte counts, and the urinary output of 17-ketosteroids in patients receiving typhoid vaccine for the treatment of psychoses. They noted a decrease in the blood lymphocytes and eosinophils and an irregular increase in the ratio of urinary uric acid to creatinine. They found no consistent effect on the urinary 17-ketosteroids and concluded that part, at least, of the effect produced by typhoid vaccine results from activation of the adrenal cortex, although they considered that other factors of toxic or immunologic nature may play a role. Arendshorst and Falls[46] followed the eosinophil response in patients given typhoid vaccine intravenously and noted eosinopenia proportional to the degree of fever produced. They stated that therapeutic benefit did not occur if eosinopenia was not induced. Rosen[47] studied

patients undergoing typhoid-vaccine therapy for uveitis and found pronounced decrease in circulating eosinophils in all instances; this was observed at 4 hours and persisted for 24 hours. He also found a great increase in the 24-hour output of 17-ketosteroids after injection of typhoid vaccine.

These effects, particularly the eosinophil response and the urinary output of 17-ketosteroids, are strongly suggestive of overaction of the adrenal cortex as part of the general biologic response to the pyrogenic agent. These changes are similar in nature and degree to those induced by administration of adrenocorticotropic hormone or cortisone. Therefore, it appears clear that, in addition to their other effects, typhoid vaccine and allied pyrogens activate the adrenal cortex. Whether this occurs through stimulation of the anterior pituitary gland to produce adrenocorticotropic hormone or by direct stimulation of the adrenal cortex is not known at present. A recent study showed that the sharp increase in 17-ketosteroids in plasma after intravenous administration of typhoid vaccine could be prevented when the febrile reaction was suppressed with aminopyrine.[48] The 17-hydroxycorticosteroids in plasma did not increase when there was no fever, although the drug failed to abolish other systemic effects of the vaccine, such as weakness and nausea. It was concluded that the action of aminopyrine on the central nervous system, by blocking the pyrogenic effect of the typhoid vaccine, prevented the stimulus to release of corticotropin (ACTH) and hence to adrenocortical activation. From this study it appears that fever is the active agent in aiding uveitis after injection of typhoid vaccine.

It is possible, though by no means proved, that activation of the adrenal cortex by fever is responsible for the therapeutic effects of foreign-protein therapy. Many of the clinical studies just mentioned apparently indicate that fever therapy acts principally, if not wholly, by activation of the adrenal cortex, with resultant increase in the production of endogenous corticosteroids. However, it should be emphasized that the administration of corticosteroid hormones and of bacterial pyrogens is associated with a number of dissimilar reactions, many of which are so diametrically opposed as to suggest that some of the effects of bacterial pyrogens and fever are unrelated to either stimulation of the adrenal cortex or increase in body temperature.

It is well known that the administration of steroids may cause a breakdown of apparently healed gastric ulcers; perforation and death have occurred in several instances. On the contrary, administration of bacterial pyrogen even in doses that do not produce fever prevents the development of experimental gastric ulcers due to histamine and may relieve the symptoms of gastric ulcer in man. Corticosteroids and fever have opposite effects on hepatic glycogenesis. Administration of corticosteroids is associated with storage of glycogen by the liver due apparently to increased gluconeogenesis arising from breakdown of protein. Fever, whether active or passive, causes glycogenolysis due to increased utilization of carbohydrate. Some reports have shown that fever increases and steroid therapy decreases the permeability of cells. Administration of steroids causes reduction in antibody titer, while fever therapy increases the titer. In addition, a number of systemic reactions that are associated with increase in body temperature do not appear with use of steroids. The reactions that occur only with fever therapy are (1) an increase of 7% in the basal metabolic rate for each degree increase in body temperature; (2) an increased systolic and decreased diastolic blood pressure, with a resultant increase in circulation that may amount to an 80% to 100% increase over normal, and (3) increased permeability of the blood vessels to large molecules during vasodilatation, which is reflected in the ease with which drugs enter the cerebrospinal fluid and, presumably, penetrate the blood-aqueous barrier.

Thorn [49] has stated, "At this moment I do not think it is fair to assume that the effects of fever therapy are necessarily due to adrenal activation and, therefore, visualize that steroid therapy and fever therapy may operate on the same end organ, but possibly by multiple approaches." Supporting Thorn in this view that foreign-protein therapy has beneficial biologic effects other than nonspecific adrenocortical stimulation are personal communications from Hughes,[50] Swan,[51] Leopold,[52] and Gordon.[53] Supporting the view that nonspecific protein therapy probably acts almost exclusively through the pituitary-adrenal axis are personal communications from Woods,[54] Maumenee,[55] Post,[56] and Dunphy.[57]

Thus, active fever therapy undoubtedly owes many of its beneficial effects to release of adrenocortical hormones. That it has other beneficial modes of action is strongly supported by some workers, but these other actions are less well recognized and their value in ocular therapeutics is not definitely known.

Clinically, passive fever therapy already has been largely discarded. When fever therapy is used now it is almost always of the active type. Probably the most widely accepted nonspecific protein used today to produce fever is triple-typhoid "H" antigen, which is favored by Woods and also here at the Mayo Clinic. Other preparations have their advocates, however. Berens [20] prefers Pyromen, which is a polysaccharide derived from Pseudomonas aeruginosa. Braley [58] uses both intravenous injection of typhoid vaccine and intramuscular injection of boiled milk and considers that they are equally efficacious. Lebensohn [59] has found that some patients respond to one form of foreign-protein therapy and not to another, and so if one type fails he tries others. He uses typhoid vaccine, given intravenously, and milk, diphtheria antitoxin, and occasionally Coley's toxin, all injected intramuscularly. However, it is probably best always to use the same product so that the physician is familiar with its characteristics and potency. This leads to more reliable results and increases the margin of safety. Fever is the reaction most easily measured and is thus used as the criterion for treatment. The opinion as to the ideal temperature to be maintained varies but generally falls in a narrow range. Woods considers the optimal temperature to be 102 to 103 F, while here at the Mayo Clinic it is considered that the temperature should not be more than 102 F, with an optimum between 100.4 and 102 F.

The dose and method of use of foreign proteins vary. In general, two methods are used currently. Here at the clinic, single intravenous injections of typhoid vaccine are given, beginning with 10,000,000 organisms; 48 hours later, the dose is increased to 15,000,000 organisms. As a rule, if the first two temperature curves are the same, the third dose is increased by 5,000,000 organisms. If the peak of the second dose is less than the first, the third dose is increased by 10,000,000 organisms. This is essentially the same regimen used by Woods, who begins with 8,000,000 to 12,000,000 organisms and increases the dose about 25% every four days. Improvement will appear within 10 days. Woods stated that four to six bouts constitute a full course and that use of more than eight bouts at any one time is contraindicated.

Another technique of fever therapy is advocated by Buxeda,[60] Curry and Shaw,[61] and Chandler.[62] It consists in the use of an isotonic solution of sodium chloride containing 1,000,000,000 to 2,000,000,000 organisms per liter and given intravenously at the rate of 20 to 30 drops per minute for 4 to 12 hours. The degree of reaction is controlled by the rate of flow. The general condition of the patient and the severity of the disease are considered in regulating the duration and severity of the reaction. If sufficient improvement does not occur after one treatment, a second continuous injection is given in 48 hours. This method of treatment is advocated by those who use it because they consider that it may be given safely to elderly and debilitated patients and

that the degree of fever and chilling may be controlled constantly.

As described by Woods,[1] the clinical reaction to an injection of a pyrogenic agent is diphasic. In the primary positive phase, which begins about 3 to 6 hours after the injection of the foreign protein and lasts 8 to 12 hours, the general symptoms may be slight to severe. The chief reactions occurring in this primary phase are fever, leukopenia followed by leukocytosis, increase in the erythrocytic sedimentation rate, and an increase in blood proteins, proteolytic and lipolytic enzymes, and serum complement. In addition, there are primary acidosis, generalized vasodilatation, an increase in capillary permeability, mobilization of preformed antibodies, a sharp increase in the titer of immune antibodies, and transient increased resistance to infection. However, in the primary phase there may be considerable increase in the local inflammation within the eye, with actual extension and spread of the local process.[1] For this reason, if the lesion is close to the macula but not yet involving it, one would be concerned about the use of fever therapy, which could cause spread of the lesion, involvement of the macula, and destruction of central vision. Occasionally, the accentuation of inflammation in the primary phase is so slight that it may pass unnoticed.

The secondary, or refractory, phase of the nonspecific protein reaction immediately follows the primary phase. It is characterized by a decrease in temperature to normal; disappearance of leukocytosis; decrease in blood proteins, electrolytes, complement, and enzymes; disappearance of the antibodies mobilized in the serum, and decrease in capillary permeability. The local inflammation decreases, usually to less than pretreatment levels; this decrease may last only a few days, or it may be more permanent and initiate a long period of improvement. After the subsidence of the primary phase, the patient is usually nonreactive to further injections of the protein for one or two days.

Fever therapy is not without danger, and several deaths have been reported during its use. These usually, but not always, have been due to large doses. In one instance, death occurred after an injection of only 10,000,000 typhoid organisms.

Special care is necessary when fever therapy is given to patients who have been receiving corticosteroids. Abrupt withdrawal of the corticosteroids after prolonged administration is followed by suppression of cortical activity, with the physiologic effects of adrenalectomy. Therefore, such patients should be exposed to fever therapy with caution. Evidence supports the assumption that endogenous secretion of corticotropin is depressed by administration of exogenous corticotropin and that adrenal insufficiency also may follow therapy with corticotropin.[63] On this basis, it appears safest not to give passive or active fever therapy to patients who have been receiving corticotropin. If fever therapy is to be given to any patient who has received any of the steroids in significant quantities within three to six months, either prophylactic steroid treatment should be given concomitantly or a steroid preparation for intravenous use should be immediately available if signs of acute adrenal insufficiency should develop.

Steroid Therapy.—The use of hormonal therapy with corticotropin and cortisone was first introduced by Hench and his associates at the Mayo Clinic in 1949. Shortly thereafter, these compounds were found to have a startling action on certain types of ocular inflammation. One of the first reports on the use of cortisone in ophthalmic diseases was by Henderson and Hollenhorst,[64] from this clinic, in August, 1950. Today there are available comprehensive summaries of the pharmacology, therapeutic action, and clinical use of corticotropin, cortisone, and hydrocortisone in both systemic and ocular disease. The most recently synthesized adrenal corticosteroids are prednisone, prednisolone, and fludrocortisone acetate. Their action also has been studied in both systemic and ocular diseases. The following

is a brief summary of present knowledge of these various hormones as related to the treatment of uveitis.

Corticotropin is produced by the anterior pituitary gland as a result of various stimuli arising from such factors as stress, infections, and injuries that probably act through the hypothalamus. Corticotropin acts directly on the cortex of the adrenal gland and stimulates production of a number of adrenal corticosteroids. Corticotropin owes its therapeutic action to these corticosteroids. It has no peripheral or local action on tissue. Corticotropin is destroyed in the gastrointestinal tract and must be given parenterally or intravenously.

Hydrocortisone is the principal corticoid in perfusates of the adrenal gland, and it is possible that other adrenal corticosteroids may be either precursors or metabolites of hydrocortisone. Hydrocortisone is less soluble than cortisone and is some 30% more potent in equal doses. The newer steroids, namely, prednisone, prednisolone, and fludrocortisone, appear to be considerably more potent than any of the other corticosteroids yet produced. Cortisone, hydrocortisone, prednisone, prednisolone, and fludrocortisone all have a definite local effect on tissues when applied topically. Cortisone, prednisone, and prednisolone are given either orally or by parenteral injection. Hydrocortisone is relatively inert when given intramuscularly and usually is administered by oral ingestion only. Fludrocortisone, because of its extremely potent side-effects when given systemically, is only used topically.

All the adrenal corticosteroids produce general metabolic and physiologic changes that vary somewhat according to the steroid used and the amount given. Chief of these changes are (1) a regulating effect on electrolytes, with retention of sodium and increased excretion of potassium and calcium, and (2) retention of water, with increase in the volume of plasma and extracellular fluid. In addition to the electrolytic effects, many metabolic changes are induced by these hormones, with effects on the mechanisms regulating proteins, fats, and carbohydrates. This metabolic action increases the synthesis of glucose from protein (gluconeogenesis), causes increased mobilization and use of fat, produces lysis of fixed lymphoid tissue with depression of circulating eosinophils, and, through its androgenic effect, may result in masculinization, hirsutism, and, finally, Cushing's syndrome. Any or all of these effects can be produced by excessive treatment with corticotropin, cortisone, or hydrocortisone. Prednisone and prednisolone also produce similar side-effects; however, their effects on electrolytes are greatly reduced, so that they cause much less excretion of potassium and retention of sodium. They do have a diabetogenic action,[65] however, and depressive psychoses also have been reported.[66] Prolonged treatment with all these corticosteroids may depress the patient's own adrenal cortex to the extent that it becomes relatively inactive. In such cases, the sudden withdrawal of exogenous hormones will precipitate acute adrenal insufficiency. Thus, when these hormones are used systemically to any appreciable degree, the patient must be under constant observation for the development of untoward symptoms.

As knowledge of these hormones and their physiologic action has grown, the list of contraindications to their use gradually has shortened until now there is no absolute contraindication to their use unless it be Cushing's syndrome. Relative contraindications or instances in which they should be used with caution include peptic ulcer, diabetes, cardiovascular-renal disease, psychoses, and tuberculosis. As already pointed out, however, ocular tuberculosis may not be a contraindication and may even be an indication for steroid therapy if appropriate antibiotics are used also. Systemic contraindications do not preclude topical or subconjunctival administration of these hormones.

Before consideration is given to the use of specific steroids in the treatment of various types of uveitis, some factors concerning the

general use of steroids in uveitis require emphasis. First of all, the rationale for the use of steroids in uveitis is based on their antiphlogistic action. Steroids, in themselves, are not curative but derive their great clinical usefulness from the protection they afford against acute inflammatory processes resulting from some physical, chemical, or bacterial agent.[67] The aim of treatment in uveitis is the preservation of the functional integrity of the eye, with retention of as much vision as possible. By their antiphlogistic action, steroids appear to interpose a shield between the cell and the inflammation-provoking agent. Because of this, the reaction of the eye to the causative agent is reduced, with less exudation, inflammation, and neovascularization; consequently, the results with regard to the functional integrity of the eye are improved. Acute choroidal lesions tend to heal with fragmentation rather than with shrinkage and pigmentation such as follow nonsteroid therapy or no therapy at all. Vitreous exudation is prevented or cleared, and, since the pigmentation is slight, the healed zones have a peculiar smeared appearance.[68]

Hogan and associates [69] observed a tendency for ophthalmologists to use steroids topically at less frequent intervals than are necessary. These authors considered that if topical therapy is instituted it should be given at least every hour during the day and that an ointment containing steroids should be used once or twice at night. Since steroids are being used on a symptomatic basis to reduce the amount of inflammation and exudation, a high concentration of steroids should be maintained on and in the tissues. In order to attain such concentrations, one should not forget the subconjunctival injection of these agents, since Hogan and associates have seen a number of cases in which the disease quieted rapidly after the institution of subconjunctival injections. The use of injections under Tenon's capsule, as advocated by Swan and co-workers,[70] is more effective than simple superficial injection beneath the conjunctiva. Gordon [71] stated that, while there are cases of uveitis in which the disease can be controlled with topical medication, it is not wise to give such therapy a trial of more than several days; if appreciable response is not exhibited within that period, he then would recommend systemic therapy. The topical use of steroids as the sole therapeutic agent in posterior uveitis is evidence of ignorance of steroidal action. Gordon [72] always employs systemic therapy in uveitis, even though the infection may be in the anterior segment, as in the case of iritis. He considered that use of systemic therapy speeds up the response and thus shortens the course of the disease to a minimum.

Another point stressed by Gordon [72] and others is that there is no such thing as a "course" of steroid therapy. The daily dose and the duration of treatment are individual in each case and depend on the response of the patient. One must employ sufficient amounts initially to suppress the disease process and then, once the response has been obtained, keep it suppressed with gradually decreasing doses until the patient is completely free of signs and symptoms when medication is discontinued. An increase in symptoms is a signal to increase the dose, whereas a decrease in symptoms indicates a decrease in dose. Steroids are ideally suited for use in ophthalmology, since large systemic doses rarely have to be continued for a long time. If large doses are used initially, suppression of the inflammatory reaction usually occurs and then the systemic dose may be gradually decreased. Topical therapy usually is employed concomitantly with systemic therapy, and the latter is continued until the patient is asymptomatic. Then the systemic dose is gradually decreased until a low maintenance level is reached, which is continued for one or two weeks. Then treatment is discontinued completely. This aids in avoiding a flare-up of symptoms caused by too early withdrawal of systemic therapy. Almost all authorities agree that topical therapy should be continued for at least two weeks after the cessation of sys-

temic therapy, even though the patient may be free of symptoms.

Reports in the literature indicate that uveitis occasionally fails to respond to steroids but subsequently responds to some other type of treatment, such as fever therapy. The causes of failure of steroid therapy are threefold. The first is the employment of only topical therapy when systemic therapy is indicated. The second cause is the use of inadequate doses in systemic therapy. If the patient does not respond to the original systemic doses, they should be increased and sustained at extremely high levels for at least seven days before the condition is considered nonresponsive to that steroid. Finally, if the disease fails to respond to one steroid, others should be tried, always including a course of corticotropin, before use of steroids is abandoned.[1,10,67,73,74] Hogan [75] has not seen a single patient with uveitis who failed to respond to steroid therapy and then subsequently responded to fever therapy. Gordon [76] has not seen more than one or two such cases. In reference to the several such cases recorded in the literature, Leopold [77] stated that benefit might have occurred after treatment with steroids if larger doses had been employed. He also pointed out that these eyes might have quieted spontaneously in time after cessation of steroid therapy and that the improvement after fever therapy might have been fortuitous.

The wide choice of steroids that are now available commercially poses the question of which one to employ. It is logical to consider cortisone first, since this was the first steroid used clinically. In treating uveitis with cortisone, Gordon [12] recommended an initial daily dose of 300 mg. A response usually is noted after one to two days, and then the dose may be reduced fairly rapidly to a daily maintenance dose of 100 mg., which is continued until signs of active inflammation are absent. Gordon considered that the dose should be increased or an alternate steroid should be employed when acutely ill patients fail to respond within approximately 72 hours. According to Hogan,[74] if an immediate response does not occur it may be necessary to increase the daily dose to 400 mg. to achieve a sustained therapeutic effect.

Use of cortisone must be continued as long as the activity of the disease indicates that vision is endangered. As the acute inflammation subsides, one may consider reducing the dose gradually. Therapy should be continued until all danger has subsided. If at any time the patient relapses and there is a flare-up in the infection, the dose is increased immediately. Gordon pointed out that in short courses, such as a week or so, use of the steroid may be discontinued fairly abruptly over a period of one to several days without fear of adrenal insufficiency. However, if the patient has been receiving systemic therapy for many weeks, it is safer to reduce the dosage gradually at a rate of 10% of the maximal dose per day. Sudden discontinuance of extremely large doses may produce rebound of the disease, whereas slow reduction under such circumstances gives far better results.

Cortisone also may be given as a subconjunctival injection; at present, this is the steroid of choice when this route of administration is used. Gordon [12] recommended injection of 0.5 ml. of a 2.5% suspension of cortisone under the bulbar conjunctiva high under the upper lid. This dose is usually effective for 3 to 14 days. The only guide for the frequency of injection is the response of the disease. The presence of white crystals under the conjunctiva does not necessarily mean that active cortisone is still present. If the patient does well on subconjunctival injections, this procedure can be utilized as a means toward decreasing systemic therapy or eliminate it completely. Gordon considered that subconjunctival injections are especially effective in the treatment of juxtapapillary chorioretinitis. Klien [78] agreed that use of corticotropin or the corticosteroids is the treatment of choice in this type of uveitis.

The next steroid that became available was corticotropin, or adrenocorticotropin. Because this hormone has no local effect, it cannot be used topically, whereas all other presently available steroids are effec-

tive when applied to the eye in drops or ointments. Corticotropin may be given either intravenously or intramuscularly. The initial intramuscular dose varies from 80 to 120 U. S. P. units per day given in four divided doses. As the disease responds, the daily dose may be reduced to 50 to 80 units; if response does not occur, the dose may be increased to 100 to 150 units per day. Children are given the same dose as are adults, unless they are less than 6 years of age, when they are given about half the adult dose. Long-acting preparations of corticotropin are available for intramuscular use. The same daily dose is appropriate, but the agent usually is given only at intervals of 12 or 24 hours, thus obviating frequent injections. As the disease responds, the dosage is adjusted until the least amount necessary to control the inflammation is found.

If therapeutic response is not observed after three or four days of intramuscular injections, then the intravenous route should be used. Intravenous administration of corticotropin is especially valuable in patients who are refractory to intramuscular injections or in whom the adrenal cortex has been severely depressed by prolonged or excessive use of corticosteroids. Intravenous administration also is indicated in patients in whom the ocular inflammation is so severe that the most intense initial therapy possible is required. It must be remembered that corticotropin stimulates secretion not only of cortisone or hydrocortisone but also of all the steroids manufactured by the adrenal cortex. It is possible that many of these little-understood steroids may have a beneficial therapeutic action in inflammation. For intravenous therapy, 25 U. S. P. units of a short-acting preparation of corticotropin may be dissolved in a liter of a 5% solution of dextrose or in a liter of an isotonic solution of sodium chloride and given as a slow intravenous drip during an eight-hour period once daily. This method of administration, according to Hogan and associates,[74] appears to be 8 to 12 times more effective than does the intramuscular method. Larger doses, such as 40 units per day, may be indicated in acute emergencies, but a dose of 25 units is adequate in most cases. After the acute process has become quiescent, the intramuscular method of treatment may be instituted.

Some patients do not respond to cortisone or hydrocortisone but attain a favorable therapeutic effect from corticotropin. Response may be delayed, however, because of the adrenal cortical suppression that may have occurred in the preliminary trials with cortisone or hydrocortisone. Woods[1] recommended that a patient should receive combined topical and systemic therapy with the adrenal corticosteroids. If a satisfactory response is not obtained, the intramuscular injection of corticotropin should be tried. If response does not occur after three or four days of such treatment, the intravenous administration of corticotropin should be employed. If response is absent after seven daily intravenous injections, hormonal therapy probably should be abandoned. If the inflammation is controlled satisfactorily, the hormonal therapy should be tapered off until, by trial and error, the minimal dose necessary to maintain the improvement has been determined. Use of this dose should be continued as long as necessary, with due precautions to detect any untoward side-effects.

Hydrocortisone possibly produces fewer effects of overdosage as compared with cortisone, apparently because of the smaller doses required to achieve a therapeutic response. It was Gordon's[71] impression that those patients already well controlled with cortisone did even better when hydrocortisone was used. In some cases, hydrocortisone succeeded when cortisone failed. Hydrocortisone acetate is relatively ineffective when given by subconjunctival injection, and cortisone is preferred by this route. Hydrocortisone is given orally in doses that are approximately two-thirds of those used for cortisone. Thus, in acute ocular conditions, the oral dose is 250 mg. the first day, 125 mg. the second day, and 70 mg. per day there-

after for one or two weeks. The daily maintenance dose is kept at about 70 mg. for the greater part of the treatment, and then it is reduced gradually. Hydrocortisone is given orally in divided doses every six hours around the clock. When a more immediate response is required, it is given intravenously. A 20 ml. ampule contains 100 mg., and this is added to 1 liter of isotonic sodium chloride or dextrose solution and given by slow intravenous drip during a period of four to eight hours. After one intravenous treatment, the obtained therapeutic response usually can be continued by oral administration of the steroid. When hydrocortisone is given systemically, concomitant topical therapy almost always is used also and is continued for at least two weeks after systemic therapy is discontinued.

The metisteroids are the newest and probably the most effective of all the corticosteroids in the management of uveitis. Prednisone is the synthetic analogue of cortisone, and prednisolone is the analogue of hydrocortisone. Leopold and associates [79] and Gordon [12] have shown that prednisone and prednisolone are two to four times more potent than cortisone and hydrocortisone in anti-inflammatory effect. Woods [1] stated that these metisteroids are four to six times as active as cortisone or hydrocortisone. In addition to their greater potency, the undesirable side-effects and toxic reactions of the metisteroids are less than those experienced with the other steroids. The retention of salt and loss of potassium and nitrogen seen with administration of cortisone apparently are minimized with the use of these new steroids. Therefore, prednisone or prednisolone is being used in preference to the other steroids for systemic therapy. When prolonged systemic administration is indicated and in order to avoid disturbances in excretion of potassium or retention of sodium and to minimize the amount of steroid used, prednisone or prednisolone is the steroid of choice, in a daily maintenance dose of 5 to 10 mg. King and co-workers [80] stated that these metisteroid compounds doubtlessly will replace cortisone and hydrocortisone in the treatment of severe ocular inflammation requiring oral therapy. Many patients with severe uveitis who have not responded to orally administered cortisone or hydrocortisone have experienced rapid and favorable results with either prednisone or prednisolone given in the same manner. Because of their greater potency and lower incidence of side-effects, Gordon [72] recommended that it is best to use one of the newer metisteroids in the initial treatment of uveitis in the absence of a previous history of steroid therapy. However, even though these drugs are ideally suited for the ophthalmologist, who usually requires short-term corticosteroid therapy, he must be cognizant of their potency and possible untoward effects during prolonged administration. He should be on the alert for complications from their use and should be sufficiently versatile to change the treatment when a prompt response is not obtained or when side-effects appear. According to most observers, the two metisteroids appear to be equally efficacious, so that there is no choice between them. According to King and associates,[80] however, prednisolone in drops or ointment appears to be slightly more effective than does prednisone.

When these agents are used, the recommended initial dose is 30 to 40 mg. per day in four divided doses, accompanied by a 0.5% suspension applied topically every hour and the ointment form used each evening. For nonresponsive patients, it may be necessary to increase the initial dose to 60 or 80 mg. per day. The initial large doses should be maintained until the patient has shown an excellent response. When this point is reached, systemic therapy should be tapered off gradually by increments of 10% per day until, through trial and error, an adequate maintenance dose is reached. With the metisteroids, this averages between 2.5 and 10 mg. per day. In acute disease, the systemic dose may be tapered off gradually and then discontinued, but if the patient relapses doses are increased immediately. It is

much wiser to give an additional week or so of low doses than to discontinue treatment too soon. The topical therapy is always continued for at least two weeks after systemic administration has been discontinued. One last point favoring use of metisteroids should be mentioned. Hogan and co-workers [69] stated that not a single instance of herpes febrilis occurred in more than 200 patients treated topically with ointments and suspensions of prednisone and prednisolone. This is contrary to experience with cortisone and hydrocortisone, although only time will indicate whether these new steroids are capable of triggering herpes.

Fludrocortisone exerts an anti-inflammatory effect 10 times greater than that of cortisone when given in equal concentrations; in addition, it has a metabolic effect 10 to 20 times that of cortisone and an effect on electrolytes 50 times greater than that of cortisone. Thus, the systemic use of this steroid is limited by its salt-retaining effect, which produces much more edema than does any other corticosteroid. In clinical use, fludrocortisone has proved effective in patients who did not respond to hydrocortisone and occasionally it proved to be less irritating. However, even when it is used topically, retention of sodium with edema has been reported. Thus, this agent is only recommended for systemic use in Addison's disease and adrenocortical hyperplasia of the adrenogenital type. Its systemic or local administration is not recommended for the treatment of uveitis.

A few specific forms of uveitis that have failed to respond to any previous type of therapy have been shown recently to respond favorably to steroids. The most important of such diseases is sympathetic ophthalmia. Steroid therapy in sympathetic ophthalmia has been more successful than has any other form of treatment thus far reported. According to a panel headed by Duke-Elder,[81] results with steroids are so encouraging in sympathetic ophthalmia that they may revolutionize the prognosis in this disease. Lavery [82] also reported good results with steroids in the treatment of this disease. Woods [1] recommended daily intravenous injection of corticotropin until the inflammation is brought under control. Topical and oral use of corticosteroids is substituted as the corticotropin therapy is tapered off. The oral dose of corticosteroids is diminished gradually until the minimal maintenance dose is determined. If untoward systemic side-effects are absent, this dose is continued over a period of months, with occasional periods of rest and injections of corticotropin to stimulate a depressed adrenal cortex. Finally, treatment can be tapered off and then terminated without recurrence of the sympathetic inflammation. Woods [1] is supported in his use of corticotropin in sympathetic ophthalmia by the findings of Laws and Howard [83] and Vesterdal,[84] who found it to be an extremely efficacious form of treatment. Winter [85] recently reported 257 cases of sympathetic ophthalmia, which is the largest series ever collected. He advised against enucleation of the exciting eye, except when this eye is blind, because he found that even prompt enucleation of the exciting eye after the onset of symptoms in the sympathizing eye did not materially affect the visual result. He also stressed that steroids provide a degree of control of sympathetic uveitis not previously obtainable with the classic methods of treatment.

The use of steroids, both local and systemic, appears to be extremely effective in endophthalmitis phacoanaphylactica, and is a valuable adjunct to surgical removal of any excessive amount of residual lens cortex if this becomes necessary.[86,87]

Another type of uveitis in which steroids are of great value is the glaucomatocyclitic crisis. In the treatment of such crises, Posner and Schlossman [88,89] emphasized that the attacks are self-limited, subside spontaneously, and leave no evidence of impairment of function no matter how great the pressure may be during the acute phase. In the presence of greatly increased tension, one is tempted to do something, either to use strong miotics or resort to operation, if only

paracentesis. Strong miotics definitely are contraindicated in this condition, as they produce pain, congestion, and spasm of the ciliary muscle. Surgical procedures do not prevent recurrence. The primary treatment should be directed against the cyclitis. Weak mydriatics probably are best at first, and 10% phenylephrine hydrochloride or 1% cyclopentolate hydrochloride can be used to prevent the formation of posterior synechiae. If the response is good and the pressure does not increase, homatropine, scopolamine, or even atropine then may be used locally. Concomitantly, one always should use one of the steroids topically to suppress the cyclitis, and this is probably the most important part of the treatment. If mydriatics are used and one is afraid of the high pressure, 250 mg. of acetazoleamide may be given concurrently every six hours to assure good control of the pressure.

The treatment of uveitis associated with herpes zoster ophthalmicus generally has been discouraging, but a recent paper by Scheie and Alper [90] cited seven authors who used steroids with good results. On the basis of 24 preliminary cases, Duke-Elder [91] concluded that systemic use of cortisone or corticotropin is indicated in the treatment of herpes zoster ophthalmicus and its associated uveitis. Scheie and Alper reported on 11 patients who had herpes zoster ophthalmicus and who were treated systemically with cortisone or corticotropin. All patients showed the classic signs of iridocyclitis, occurring alone or accompanied by keratitis. As in Duke-Elder's patients, the relief of pain was uniformly dramatic, the discomfort nearly always disappearing in 24 to 36 hours. Inflammatory ocular signs showed great improvement, although a protracted mild but recurrent course ensued in several instances. These symptoms of rather mild iritis were controlled readily by local use of atropine and cortisone. An increasing number of reports suggest that corticosteroid or corticotropin therapy is of great value in this condition. These hormones in some way probably block the response of the tissue to the viral agent, thus suppressing the ocular reaction and preventing the serious complications ordinarily encountered in this condition. It is unlikely that the steroids have any specific action against the virus of herpes zoster.

Another form of uveitis that has been resistant to treatment but in which steroids show promise is the type associated with sarcoidosis. A large number of agents have been used in the past, including antibiotics, sulfones, radiation, mechlorethamine, and, more recently, calciferol and dihydrotachysterol. Careful evaluation and follow-up studies on patients so treated demonstrated that such therapy has been of little value in sarcoidosis. Intensive treatment with corticotropin, either with the long-acting gel or by intravenous drip, and the parenteral or oral administration of the adrenocorticosteroids have been followed in some cases by almost complete regression of the lesions. On the termination of treatment, approximately 50% of the favorably reacting patients showed prompt recurrence of the clinical symptoms, denoting that prolonged therapy with a low maintenance dose is usually necessary. Woods [1] reported several cases in which, after initial control of the ocular lesions by intensive corticotropin therapy, the topical use of corticosteroids in the eyes appeared sufficient to prevent local relapse, although recurrence of cutaneous and mediastinal lesions was noted.

Hertzog [92] recently reported on a patient who had Boeck's sarcoid with systemic manifestations and a nodule in the left iris associated with all the signs of active iridocyclitis, such as extensive keratic precipitates, flare and cells in the anterior chamber, scattered particles of pigment on the lens, and some posterior synechiae. For those who are reluctant to use systemic steroid therapy because of the risk of complications, this case is especially worthy of consideration in view of the large doses and the uncomplicated course. As has been mentioned previously, the usually accepted adequate initial daily dose of prednisone in uveitis is 40 mg. This patient received 35 mg. of prednisone by mouth every 6 hours,

or 140 mg. per day, which is three to four times the usual amount; this dose was increased gradually to 50 mg. every 6 hours by the 10th day, or five times the usual dose. Treatment was terminated on the 14th day, a rather rapid withdrawal from a regimen of large doses of steroids. The patient showed no ill effects during treatment or afterward. The weight remained essentially unchanged. Values for serum albumin, globulin, calcium, phosphates, sodium, chloride, and alkaline phosphatase remained normal. No local therapy was used except drops of 2% atropine given daily. Because of these large doses of steroids, the patient was given antacids, antispasmodics, supplementary potassium, and a low-sodium diet. The results of treatment in this case after two weeks included almost complete absorption of the nodule in the iris, almost complete clearing of the flare and cells, absence of the previous lymphadenopathy and calcification, and roentgenologic evidence of reduction in size of hilar nodes. The uncorrected vision remained 20/20 in both eyes, and the tension remained normal. In the absence of any other effective or specific therapy, intensive use of steroids appears thoroughly justified in ocular sarcoidosis. It is possible that prolonged oral use of small doses of prednisone also may be useful in preventing recurrence and protecting the eyes once the initial symptoms have been controlled.

Optimistic reports on the use of steroids in the Vogt-Koyanagi-Harada syndrome [93-95] have appeared in which dramatic results with corticotropin or corticosteroids, used systemically or by subconjunctival injection, have been claimed. However, Cordes and Swartz [96] reported only slight benefit from steroids in this condition. At present, the efficacy of steroid therapy in this syndrome is not clearly defined but it appears to be the only treatment that offers any hope of benefit.

Uveitis associated with chickenpox [97] and serum sickness [98] has been reported recently, and this complication appears to have been greatly benefited by use of steroids.

Refractory Types of Uveitis

At least four types of uveitis are known to be refractory to treatment, either specific or nonspecific.

Torula Uveitis.—The fourth instance of this type of uveitis was recently reported.[99] All patients have had associated meningitis and have died in spite of all attempts at therapy.

Leptospiral Uveitis.—In uveitis of this type, the only measures that may prove to be of any value whatever are fever therapy and local procedures, such as use of cycloplegics and paracentesis.[100] Tetracycline (Tetracyn) has been reported [101] of value in systemic leptospirosis, as has a combination of tetracycline and penicillin,[102] but no reports have been published concerning their use in leptospiral uveitis, probably because of its rarity. It is generally held that there is no beneficial form of treatment for this type of uveitis at present.

Behçet's Syndrome.—Steroid treatment is contraindicated in this condition, since it increases the clinical manifestations and decreases the antibody titer in the blood. All forms of treatment have proved futile in preventing the progression of this malignant relapsing iridocyclitis.[103,104]

Fuchs' Heterochromic Cyclitis.—In a recent review, Kimura and associates [105] pointed out that there is no known treatment for heterochromic cyclitis. Corticotropin and the adrenocorticosteroids, whether administered topically or systemically, are of no value. The cataracts are removed easily and the eye tends to respond well to surgical trauma in spite of the active cyclitis. The glaucoma that often occurs as a complication is treated by the usual methods; however, it may prove to be extremely refractory to treatment.

Survey of Present Modes of Treatment

As knowledge on the subject of uveitis increases, it is hoped that the group in which

the cause is unknown will shrink and eventually disappear, so that little need will exist for the types of nonspecific therapy which have just been described. Only when knowledge of the etiologic factors is such that all treatment may be given on a rational specific basis can the problem of uveitis be said to be solved. Until this Utopian goal is reached, nonspecific therapy will continue to occupy an important place in the management of uveitis. Probably the greatest controversy in the field of uveitis today is which of the two main forms of nonspecific therapy to use, namely, the time-honored fever therapy or steroid therapy.

It is known that direct administration of corticosteroids is far more effective in suppressing inflammatory response than is passive or active fever therapy.[39] Use of corticotropin or adrenocorticosteroids unquestionably is to be preferred to active fever therapy if the only beneficial action of fever therapy is the endogenous production of adrenocorticosteroids. However, if the induction of fever has beneficial actions on ocular disease independent of adrenal function, then it may continue to have a definite place in ophthalmic management. Since the answers to these questions are not known at present, conclusions must rest on a survey of clinical response to these two forms of therapy as recorded by those who have had extensive experience in the management of uveitis. No one has used fever and steroid therapy alternately in a series of cases, nor is this likely to be done. Even if this were done, each patient with uveitis varies so tremendously from the last that considerable doubt still would remain unless such a series were vast.

Steroid therapy has been given in uveitis for a sufficient period that the results of its use can be compared with the results of fever therapy. In an attempt to crystallize the latest thinking on the management of uveitis, I have just finished a survey among outstanding ophthalmologists of the English-speaking world. Each ophthalmologist was asked his views concerning the present status of foreign-protein or fever therapy in ophthalmology and how its efficacy compared with that of the steroids in the management of uveitis. The response to this survey was most gratifying, and the pertinent segment of each personal communication is as follows:

James E. Lebensohn (Northwestern University, Chicago): The steroids have become popular, as they are simpler to administer and occasion no discomfort to the patient. However, I believe the results with intravenous typhoid vaccine are immediately more dramatic and its use entails less expense to the patient. Many patients who have not responded to steroids have responded to the use of intravenous typhoid vaccine. Some patients will respond to one form of foreign-protein therapy and not to another. I recall one patient who developed uveitis after cataract extraction. Typhoid vaccine produced no effect but the eye became better after the first injection of milk. In another case of nongranulomatous iritis, the injection of typhoid vaccine did no good nor did the injection of milk, but the intramuscular injection of diphtheria antitoxin resulted in a prompt cure. I have also used Coley's toxin intramuscularly in stout individuals in whom intravenous medication was difficult. It has worked well, but unfortunately produces considerable after-pain, after the effect of the procaine, in which it was diluted, wears off. Since it takes 1 to 3 hours for fever to develop after a typhoid-vaccine injection, the treatment can be given in the office, which I have done for over 30 years.

A. E. Braley (State University of Iowa, Iowa City): I have always liked to use fever therapy in the treatment of uveitis and I do not feel that it will ever be completely replaced by steroid therapy. I have always used two types of fever therapy; one is intravenous typhoid H antigen and the other is intramuscular injections of boiled milk. Of recent years, of course, we have used more steroids but fever therapy is still a very good treatment and I am very fond of it.

THOMAS J. KIRBY (Mayo Clinic, Rochester, Minn.): Both foreign-protein therapy and steroid therapy are used. There is a general tendency to employ intravenous injections of typhoid vaccine or intramuscular injections of milk whenever practical, rather than intensive or prolonged steroid therapy. The use of foreign protein can be controlled therapy. It can be intensive and of sufficient duration to benefit most patients who have uveitis. The rest and regular hours of the hospitalization may be an intangible but definite aid to the remission of uveitis. Patients receiving steroids orally or intramuscularly need close supervision if the dangers of hypercortisonism and a depressed adrenal cortex are to be avoided. It is difficult to supervise the ambulatory patient. Many of our patients live some distance from Rochester, so that it becomes impossible to give these people the close observation needed if they are to receive steroids for any duration of time.

PAUL A. CHANDLER (Boston): I believe most people now use the steroids instead of fever therapy because it is so much simpler and easier. I still feel that there is a definite place for fever therapy, particularly in acute fulminating disease. I can remember several patients who did not do much on adequate doses of steroids but who had a fine response to fever therapy.

DERRICK VAIL (Northwestern University, Chicago): There is no doubt that the use of steroids in the treatment of uveitis has decreased the use of foreign-protein therapy or artificial fever. However, I have not discontinued the use of the latter and have leaned heavily upon it in certain cases in which I felt that the steroids were not doing the full job, particularly when I was afraid of recurrence on discontinuing the use of the steroids. Actually I believe that a combination of the two forms of treatment will turn out to be the best in the end.

CONRAD BERENS (The Ophthalmological Foundation, Inc., New York): There has always been a controversy on the place of foreign-protein therapy in the treatment of uveitis and I have never been a great believer in the massive doses as they were given for treating uveitis. However, in the cases which tend to become chronic, I often do use nonspecific protein therapy because I believe that, in addition to attempting to control the inflammatory process, which you can sometimes do with the steroids and atropine and with mental and physical rest, it is important to raise the nonspecific resistance.

WILLIAM F. HUGHES (University of Illinois, Chicago): In some cases with a typical appearance of acute nongranulomatous anterior uveitis, we will begin treatment directly with corticosteroids locally. On the other hand, some granulomatous-appearing lesions might suggest a certain etiology so that specific therapy may be instituted. If we have no leads as to etiology at all, and the lesion looks granulomatous in type, and we do not care to give a shotgun type of antibacterial therapy, then we usually use foreign-protein therapy.

W. M. GRANT (Harvard Medical School, Boston): I believe that the general feeling here favors employing steroid therapy first and if this is unsuccessful then trying proteins. In some cases the second form of treatment seems to work even when the first has been unsuccessful.

MILTON L. BERLINER (New York University, New York): Regarding the treatment of uveitis, I prefer the use of steroids to foreign-protein therapy. We have had excellent results using steroids, with none of the changes inherent in fever therapy. A few years ago there was a death in New York City following an intravenous injection of 10,000,000 typhoid organisms.

PROF. G. I. SCOTT (University of Edinburgh, Edinburgh, Scotland): I think it would be fair to state that in general in this country fever therapy has been replaced by the use of steroids, although in one or two instances I know that experienced ophthalmologists have been disappointed with the results of cortisone therapy in chronic posterior uveitis, and have reverted to fever

therapy in such cases. Our practice here at the University of Edinburgh is, in the main, to use steroid therapy but occasionally in cases which are not responding we revert to the old fever therapy.

KENNETH C. SWAN (University of Oregon, Portland): Neither fever nor foreign-protein therapy has been used in the treatment of uveitis by our faculty for the last 2 years. During this time we have been using and investigating corticosteroids in treating uveitis.

PROF. ARNOLD SORSBY (Department of Ophthalmological Research of the Royal College of Surgeons of England, London): Fever therapy as such has never had much vogue here. The various pyrogenic agents that have been advocated from time to time have found little enthusiasm. Foreign-protein shock from the use of milk or typhoid vaccine has been practiced more widely in a vague belief that there is some virtue in the protein shock, whatever that may be. The advent of ACTH reduced such enthusiasm as existed for these methods to a still lower point. The reaction from ACTH has brought back protein shock to some extent. There is, I think, no clear teaching or practice on protein-shock therapy. Its use is a last resort in the expectation that nothing very much will follow. I have tried to give an account of current practice. As to my personal views, I am afraid I regard protein-shock therapy as a first cousin of placental implants, vitamin therapy, calcium therapy, and the rest of the tribe.

LAWRENCE T. POST (Washington University, St. Louis): My own impression is that steroids and fever therapy are essentially comparable in action and that the fever part of the reaction is relatively unimportant. Therefore, we no longer use typhoid vaccine. I do agree with many other observers that posterior uveitis is essentially unaffected by either form of therapy, and that both forms are rather dramatically effective in the anterior varieties.

IRVING H. LEOPOLD (University of Pennsylvania, Philadelphia): There is no doubt that the usefulness of bacterial pyrogens in ophthalmic disease has been restricted by the apparent success of ACTH and various steroids. However, foreign-protein therapy is inexpensive and has only a few undesirable side effects; its possible actions other than that of release of steroids mean that it should still be considered as of potential value in ocular diseases.

DAN M. GORDON (Cornell University, New York): With the advent of steroid therapy, I find that I am able to handle practically all of my patients with uveitis on an ambulatory basis using topical and/or systemic therapy. I have had not over one or two patients in the past 7 to 8 years who have succeeded on fever therapy after having failed on short courses of steroids. In an occasional rare case I have used typhoid vaccine to help as a "tapering-off" procedure after steroids. I have not found concomitant fever-steroid therapy of any special value. On the whole, I now use fever therapy but rarely. Often when I have tried to switch patients with chronic uveitis from steroids to typhoid vaccine, I have gotten relapses, even though the patient had long-sustained fever and chills. I am speaking about chronic uveitis. Most patients with recent acute anterior uveitis will respond to topical steroid therapy. About 25 to 35 per cent of this type require additional systemic therapy.

PROF. W. J. B. RIDDELL (University of Glasgow, Glasgow, Scotland): Taken by and large, I think that fever therapy is still used to a large extent throughout the whole country, but the steroids are more readily available at teaching and research centers and, consequently, are tending to replace the older procedures.

HAROLD G. SCHEIE and FRANCIS H. ADLER (University of Pennsylvania, Philadelphia): We have not given any type of fever therapy for several years. The omission of this therapy began not too long after our employment of steroid hormones. We never institute steroid therapy until the patient has had at least preliminary studies, particu-

larly cutaneous sensitivity tests, whose reliability would be of no value after the use of systemic hormones. If tests for tuberculosis are positive or some other systemic ailment is found, we do not use steroid hormones but use more appropriate therapy.

JOHN H. KING JR. (Washington Clinic, Washington, D. C.): I have employed typhoid vaccine and also the artificial Hypertherm cabinet only four or five times during the past 3 years, whereas fever therapy was almost routine prior to that time. The value of fever therapy has been mostly replaced by the corticosteroids, especially the newer metisteroids, in nongranulomatous uveitis. In instances where steroids are not effective for the type of intraocular conditions known to respond ordinarily, I would not hesitate to use fever. If steroids are contraindicated or cause severe toxic side effects, one might consider the use of controlled fever therapy. A recent case of severe plastic iridocyclitis, probably on the basis of gonorrheal allergy, showed no response to 10 days of intensive oral and local therapy with prednisolone. One intravenous injection of typhoid vaccine was given and this resulted in immediate improvement. Prednisolone was again administered and improvement continued and remission was maintained. Apparently the typhoid vaccine was necessary to "trip the balance." This might have occurred with intravenous use of prednisolone, which was not tried.

MICHAEL J. HOGAN (University of California, San Francisco): I have no objection to the use of fever therapy for patients with iridocyclitis or chorioretinitis and I am aware some patients might respond to this form of treatment and not to corticosteroid therapy. We have attempted to treat our cases with corticosteroids in order to evaluate their use more easily. Therefore I have completely given up the use of fever therapy until we achieve our goal. I have had the experience of seeing a number of patients who had been treated with both fever therapy and corticosteroids and not seeing either method of treatment benefit the patient. So far I have not seen a case that failed with steroid therapy but subsided with fever therapy.

EDWIN B. DUNPHY (Harvard Medical School, Boston): I realize there is a controversy on the role of fever or foreign-protein therapy in the treatment of uveitis, especially since steroids have been used. At this institution we give very little fever or foreign-protein therapy now, since we feel that the steroids are much more useful and efficacious. However, there are a few cases in which steroids have not worked very well and typhoid injections have, perhaps because they call forth other unknown factors.

FRANK W. NEWELL (University of Chicago, Chicago): Currently we are using only steroid therapy and have not used bacterial pyrogens or artificial fever in the past 3 years.

ALAN C. WOODS (Johns Hopkins Hospital, Baltimore): I believe that the use of nonspecific protein therapy has been largely supplanted by the use of steroids. I am far from being in sympathy with the promiscuous use of steroid therapy, especially in granulomatous uveitis. This I have endeavored to emphasize in my recent book. Nonspecific therapy with foreign proteins still has a place in certain forms of uveitis, but with the introduction of specific antibacterial therapy, and nonspecific steroid treatment, I believe its present use is somewhat limited.

JOHN H. DUNNINGTON (Institute of Ophthalmology of the Presbyterian Hospital, New York): It is my impression that fever therapy is being used much less than formerly. Personally, I reserve fever therapy for cases in which steroids are contraindicated.

F. BRUCE FRALICK (University of Michigan, Ann Arbor): It is our feeling that foreign-protein therapy, given in the form of typhoid H antigen intravenously, does exactly the same thing as steroid therapy but much less effectively and with much more discomfort and danger, of course, to the patient. We have in the past lost patients

from foreign-protein therapy, but also in the early days of steroid therapy we lost patients from its use as well. Certainly we do not use foreign protein to a great extent any more, and only in the chronic forms of disease, where we have tapered them off from the steroids, is foreign protein usually used. I still think it is a good adjunct to our treatment and one which we should not lose sight of, in view of the fact that some people cannot be carried on steroid therapy and yet they need such measures in some form.

DAVID G. COGAN (Harvard Medical School, Boston): I have always been led to believe, by George Thorn's group, that fever did nothing more than what could be accomplished by steroids, but I know there are selected clinical cases which suggest this is not true.

SIR STEWART DUKE-ELDER and E. S. PERKINS (Institute of Ophthalmology, University of London): Since the advent of cortisone, the use of foreign-protein therapy has diminished greatly here and is now only used occasionally in cases which appear to be resistant to steroid therapy. We personally still feel that it has a small place in treatment, but we must confess that we rarely prescribe it. I think you can take this view as the general British practice.

FREDERICK C. CORDES (University of California, San Francisco): I am aware of the fact that at the present time the use of the steroids has almost completely done away with the use of foreign-protein therapy in the care of uveitis. Like most of our old tried and true remedies, I feel there are certain times when the modern methods are of no avail, that the older treatment is useful. I have this feeling with regard to typhoid therapy in uveitis that does not respond to the steroids. It is quite obviously difficult to evaluate this without a large group of carefully controlled cases, but it has been my impression in a few patients that typhoid therapy helped where the other did not.

BERNARD BECKER (Washington University, St. Louis): Since the advent of steroid therapy (and even before that), we have not used foreign-protein therapy in the treatment of uveitis.

Conclusions

Since the cornerstone of successful and rational treatment depends on an accurate diagnosis, every effort should be made to establish the exact cause in all cases of uveitis.

Separation of uveitis into granulomatous and nongranulomatous types, if possible, may be of help in ordering the diagnostic survey and in formulating principles of treatment.

It is important for the ophthalmologist, not the internist, to captain the diagnostic team, so that he may channel the diagnostic tests in certain directions commensurate with his knowledge of uveitis and its clinical manifestations.

If a positive or presumptive etiologic diagnosis is made, the treatment of choice is specific therapy when it is available. When the exact cause cannot be ascertained or specific therapy is not available, one of the nonspecific forms of treatment should be used.

Since the advent of steroids, fever therapy has been used less frequently. It is the experience of some ophthalmologists that few patients who have uveitis respond to fever therapy after failure with adequate doses of steroids. Fever therapy generally requires hospitalization while steroids may be used on an ambulatory basis. The financial saving to the patient is considerable and he is also spared the physical discomfort of fever.

Steroid therapy is efficacious because of the antiphlogistic action of these agents, with suppression of exudation, neovascularization, and scarring. The most promising steroids at the present time appear to be the newer metisteroids, namely, prednisone and prednisolone. It appears that failure in the administration of steroids frequently is

due to use of topical therapy when systemic therapy is actually required or to the use of inadequate systemic doses.

A personal survey taken among 30 outstanding ophthalmologists of the English-speaking world reveals that three prefer fever therapy over steroids. Four use both forms of nonspecific therapy and indicate no preference between the two. Twenty-three of the ophthalmologists prefer the use of steroids to fever therapy; of these, fourteen use steroids almost exclusively and rarely resort to the use of fever therapy. Thus, the majority of outstanding ophthalmologists in this survey prefer steroid therapy and generally agree that fever therapy should be reserved for patients who fail to respond to adequate doses of steroids or for those few patients in whom steroids are definitely contraindicated.

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Syndrome of External Ophthalmoplegia, Ataxia, and Areflexia (Fisher)

Ocular Manifestations in Acute Idiopathic Polyneuritis (Guillain-Barré Syndrome); Report of Two Cases

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In July, 1956, Fisher[1] described three cases of an acute illness characterized by total external ophthalmoplegia, severe ataxia, and areflexia. He noted that this syndrome was related to acute idiopathic polyneuritis. The presenting symptoms and signs in these cases were alarming until the benign course of the disease was realized. It was his report that enabled us to recognize the nature of the illness in our cases. Fisher was unable to find specific reports of similar cases. We think that individual instances belonging to this group merit description, and two such cases are here presented.

CASE 1 (The first patient was referred by Dr. Arthur B. King).—A 38-year-old white male construction worker enjoyed good health until Oct. 24, 1956, when he developed a sore throat. This progressed despite two injections of penicillin given during the next two days. Although he felt bad, he continued working. He remained in bed on the third and fourth days of the illness. He felt somewhat better on the morning of the fifth day, and he returned to work in spite of a residual hacking cough. On the sixth day he worked unusually hard pouring concrete. He felt well on retiring that evening except for some fatigue. On awakening on the seventh day there was an abrupt onset of dizziness and diplopia. The dizziness, not particularly severe initially, progressed over the next few hours so that by noon he was barely able to walk. Although he was comfortable when he was quite still and his eyes were closed, any movement of the head made him extremely dizzy. The muscles of his chest and arms were sore. Numbness migrated from his finger-tips throughout the chest, shoulders, and right side of the face. There was no headache. Inability to walk without support was attributed to loss of equilibrium rather than to weakness in the extremities. Objects seemed to dance before his eyes whenever he moved his head. He grew worse for about four days after the onset; then his condition became static for about a week, and thereafter he gradually improved.

The patient was hopitalized at Wellsborough, Pa., on the seventh day of illness. Because his ataxia progressed to the point where he was unable to rise up in bed, he was transferred to the service of Dr. Arthur B. King on the 10th day. At that time the patient was able to speak. There was no headache or vomiting. He blinked his eyes in an effort to correct diplopia. Temperature, pulse, respirations, and blood pressure were normal. The neck was not stiff. On attempting to walk, he was unsteady and swayed in all directions. He could not voluntarily move his eyes in any direction. The eyes were straight in the primary position. The pupils were round, equal in size, and reacted promptly to light and in accommodation. The fundi and visual fields were normal. There was mild bilateral ptosis. There was a history of long-standing low-grade ptosis on the left when he was fatigued. With the exception of depressed reflexes in the legs, no other abnormalities were noted on examination.

Received for publication Jan. 24, 1957.

From the Wilmer Ophthalmological Institute of the Johns Hopkins University and Hospital.

X-rays of the chest and skull were normal. Routine blood and urine examinations were normal, and the Wassermann test was negative. A lumbar puncture revealed normal pressure; clear fluid containing six lymphocytes, and 45 mg. protein per 100 cc., and a negative Wassermann test. Neostigmine bromide U. S.P. was injected, up to 2 mg., intramuscularly, but produced no change in the ophthalmoplegia. On the 10th day slight improvement in ocular motility began, and this gradually increased so that by the time of discharge downward motion seemed normal, but upward motion remained limited. Horizontal movements of the eyes improved slightly as well. The pupils remained active, and the ptosis had lessened. The unsteadiness essentially disappeared. There was no ataxia, and the Romberg sign was absent. A second lumbar puncture, on the 20th day, showed only four cells, with a protein level of 50 mg. per 100 cc. On the same day, some numbness developed on the right side of the face, and within a few hours there was partial bilateral facial weakness of the peripheral type. The facial palsy improved, but the patient was still unable to whistle at the time of discharge from the Guthrie Clinic.

Past History.—There was no history of diptheria, and the patient did not know whether or not he had been immunized against diphtheria. He had received routine Navy immunizations, including a vaccination for smallpox. He had had a reaction to horse serum administered as tetanus antitoxin in childhood. His only previous hospitalizations were for cellulitis of the left foot and traumatic fractures. The patient had been in the construction business for 18 years, and he had moved from his home in West Virginia to Pennsylvania four months prior to the onset of the illness.

Family History.—This was negative except for one sister who noted marked diminution in vision 15 to 20 years ago, attributed at that time to "rheumatic fever," but who sustained a complete recovery.

Examination (Nov. 23, 1956).—Vision in the right eye with correction was 20/15, and vision in the left eye with correction was 20/20. He read Jaeger-1 print at 30 cm. with each eye without correction. Externally, there was bilateral ptosis, with the right palpebral aperture measuring 8 mm. and the left measuring 7 mm. The corneae, corneal reflexes, tactile tension, anterior chambers, pupillary reflexes, and facial sensation were normal. The pupils measured 2 mm. bilaterally, and both reacted to light and in accommodation. There was an almost complete bilaterally symmetrical external ophthalmoplegia, however, with the eyes unable to go beyond 10 degrees on levoversion, 5 degrees on dextroversion, and 10 degrees on elevation, but with depression of 45 to 50 degrees. The symmetry of the ophthalmoplegia was confirmed by normal measurements in the primary position with the Maddox rod. Although the facial diplegia had improved, there was definite weakness of the orbicularis oculi bilaterally.

Slit lamp examination and ophthalmoscopy gave normal findings bilaterally. The visual fields were normal to 6/330 white and 3/1000 white bilaterally as well.

Additional Clinical Findings.—An atraumatic lumbar puncture, his third, on the 13th day of illness, disclosed a crystal-clear fluid under pressure so low that the manometer would barely fill, containing three mononuclear cells per cubic millimeter, with a 1+ Pandy test, a first-zone mastic reaction, and a total protein of 72 mg. per 100 cc.* A hemogram disclosed a hemoglobin level of 14.7 gm. per 100 cc.; hematocrit level, 46 mm.; sedimentation rate, 15 mm. in an hour; icteric index, 7.5, and normal platelets. WBC count was 16,150, with 62% polymorphonuclear cells, 3% eosinophiles, 32% lymphocytes, and 2% monocytes. Heterophile agglutinins were 1:10 (unabsorbed), and treponema immobilization test was negative.

The patient returned on the 60th day of illness and showed a dramatic improvement

* The normal spinal fluid in this laboratory is approximately 20 mg. per 100 cc., and 40 mg. is considered definitely upper normal. A level of 50 mg., frequently considered as upper normal, is definitely a pathologic finding here.

in ocular motility to almost normal limits. A lumbar puncture on the 60th day disclosed crystal-clear fluid with normal pressure and manometrics, no cells, and a total protein of 42 mg. per 100 cc. Inoculations of HeLa cells with cerebrospinal fluid on both the 13th and 60th days for virus culture were negative.

The patient was seen by Dr. Frank R. Ford for neurologic evaluation and by Dr. M. L. Williams for otologic examination, audiometry, and vestibular testing. Dr. Ford agreed that the patient represented the clinical picture described by Fisher and that the patient was improving rapidly. Dr. Williams noted normal subjective symptoms of nausea and dizziness on vestibular stimulation but found that the nystagmus elicited was partially inhibited in both amplitude and duration.

CASE 2 (The clinical notes on the following case were furnished by Drs. Donald L. Somerville and Frank R. Ford).—A 63-year-old white salesman was in good health until approximately March 1, 1956, when he developed coryza and a mild sore throat, which persisted for two to three weeks, despite various medications, including one injection of penicillin. On March 31 he noted the onset of tingling in the hands on awakening. The following morning he noted difficulty in bringing up mucus and also had regurgitation of fluids through the nose. His speech became affected, and diplopia, more marked on upward gaze, appeared. Although unsteady on his feet, he had no weakness in his extremities. He had no pain, ptosis, or difficulty in swallowing.

He was hospitalized on the 33rd day (April 3, 1956), and examination disclosed good visual acuity and normal visual fields. The striking finding was a marked bilateral external ophthalmoplegia, which was perfectly symmetrical. Ptosis was absent initially. Upward gaze was completely lost bilaterally; lateral movements were grossly impaired, but downward movement was almost normal. Diplopia was present in all fields of gaze. There was no nystagmus, facial weakness, or deafness. The voice was hoarse and extremely nasal, and the soft palate was paretic on phonation. The station and gait were unsteady, although no weakness in the extremities was noted. The tingling in his hands was not associated with any demonstrable sensory loss. The deep tendon reflexes were absent, but the plantar responses were normal.

He remained afebrile throughout his hospital stay. On April 16, the 46th day, a bilateral peripheral type of facial paralysis was noted. Examination at that time disclosed miotic but reactive pupils. Vision and fields were considered normal. Ophthalmoscopy disclosed no abnormalities. There was ptosis of the right upper lid, however, and upward gaze was absent. There had been some improvement in lateral gaze. On right lateral gaze, each eye crossed the midline. On left lateral gaze, there was fairly normal abduction of the left eye but no adduction of the right eye. Convergence could not be elicited. The diplopia persisted. Bilateral peripheral facial paralysis was present, but there was no sensory loss on the face. There was no deafness. The soft palate remained paretic and the voice nasal in quality. The other functions of the cranial nerves were intact. The extremities were strong, and, although the heel-knee test was well done, there was a slight tremor on finger-to-nose test bilaterally. Sensory loss could not be demonstrated in the extremities despite persistence of the paresthesiae. Areflexia persisted.

The patient gradually improved, and he was discharged on the 56th day. By the 88th day he had made an almost complete recovery and the only residuum was diplopia on forced upward gaze. His only difficulties at that time were interscapular pain and a strange complaint that the palms of his hands had become exteremly soft. Examination disclosed that all cranial nerves were intact. Although there was some diplopia on vertical gaze, there was no obvious limitation of extraocular movement. The bilateral

facial palsy had vanished; the voice was clear, and the palatal paralysis had cleared. The station and gait were normal; no weakness or ataxia was found. A fine, rapid tremor of the hands was still evident. Although the numbness of the hands had cleared considerably, the palms were interesting in that they had become so soft that they felt like velvet. The tendon reflexes had returned and were normal.

By the 159th day, he was asymptomatic except for some cutaneous hyperesthesia of the lower thoracic segments and some numbness in the great toes, back, and flanks.

Additional Clinical Findings.—Hemogram on the 34th day disclosed a hematocrit of 52 mm., hemoglobin 16 gm.; WBC count was 7750, with 83% polymorphonuclear cells, 14% lymphocytes, 2% juvenile forms, and 1% mononuclear cells. Urinalysis, chest and skull films, and electrocardiogram were normal. Tests for heterophil agglutinins were negative.

Lumbar puncture on the 34th day revealed an opening pressure of 210 mm., closing pressure 150 mm. The clear fluid contained one mononuclear cell per cubic millimeter, trace Pandy reaction, and total protein of 50.7 mg. per 100 cc. Sugar was 71 mg. and chloride was 125.6 per 100 cc.

On the 46th day lumbar puncture revealed an opening pressure of 190 mm., closing pressure 90 mm.; the fluid was clear and contained no cells, but the total protein was 97.5 mg. per 100 cc. Sugar was 105 mg. and chloride 128 mg. per 100 cc.

On April 9, 1956, neostigmine methylsulfate, 1.5 mg by injection, produced no objective or subjective improvement in the symptoms.

Comment

Before discussion of the cases, some mention of the Guillain-Barré syndrome is pertinent. The terminology of this syndrome is confused by a multiplicity of terms. Those most comonly employed are the following: Guillain-Barré syndrome, acute infectious polyneuritis, polyneuritis with facial diplegia, infectious polyradiculoneuronitis, acute idiopathic polyneuritis, and polyradiculoneuronopathy. Despite some objections, the title Guillain-Barré syndrome has the advantage of widespread clinical usage and will be employed here. The disease is of unknown etiology and is characterized by the acute onset of symptoms involving the peripheral and cranial nerves. It is slightly commoner in the third and fourth decades and possibly slightly commoner in males. A history of a preceding upper respiratory or gastrointestinal tract infection is obtained in about two-thirds of the cases, and the neurologic symptoms follow after an interval of 5 to 12 days. Weakness of the lower extremities is noted first, and this extends within 24 to 72 hours to the upper extremities and facial muscles. Sensory changes are usually not prominent, although paresthesiae may precede the weakness and cutaneous hypesthesia and impaired vibratory sense are present in about one-third of the cases. Merritt [2] points out that facial diplegia occurs in 85%, dysphagia or dysarthria in 50%, and 11th nerve involvement in 20%, but he states that involvement of the extraocular muscles is infrequent. In Haymaker and Kernohan's [3] series of 50 autopsied cases, 12 had involvement of the third, fourth, or sixth cranial nerves. Papilledema [4] is infrequent but occurs, and it has been attributed to increased intracranial pressure resulting from respiratory insufficiency or compromise of cerebrospinal fluid reabsorption by high protein content.

Walsh [4] points out that the ocular signs of the Guillain-Barré syndrome include total external ophthalmoplegia, lagophthalmos and its sequelae in facial diplegia, isolated extraocular muscle palsies, pupillary abnormalities, paralysis of accommodation, optic neuritis, and papilledema. He noted two instances with papilledema—one patient had a spinal fluid pressure of 600 mm., with a protein of 470 mg. per 100 cc.; the second had a pressure of 400 mm. and a protein of 200 mg. per 100 cc. A subtemporal decompression was necessary in the first case.

Motor weakness in the trunk and extremities is usually severe in the Guillain-Barré

syndrome. It is at times greater in the proximal parts of the extremities. In about 25% of the cases a flaccid quadriplegia with respiratory muscle involvement necessitates use of a respirator, and respiratory failure usually occurs from 2 to 21 days after onset of symptoms. Superficial reflexes as well as deep tendon reflexes are usually absent. Rapid pulse, low-grade fever, and hypertension have been noted in some severe cases.

The occurrence of external ophthalmoplegia in the course of acute infectious polyneuritis has long been known, but it usually was seen only in those cases with marked motor paralysis in the extremities. Collier[5] in 1932 described three clinical forms of the disease: (1) quadrilateral peripheral neuritis with external ophthalmoplegia; (2) quadrilateral peripheral neuritis with facial palsy and bulbar signs; (3) Landry's ascending paralysis. With regard to the first group, Collier stated: "external ophthalmoplegia . . . which is apyrexic, painless, and with rapid onset. In some of the cases, the ophthalmoplegia is severe and may be absolute so far as the external muscles are concerned, the internal muscles escaping while the limb paralysis may be slight, only showing itself by a weakness of the extensors of the periphery with an absence of reflexes. In other cases, the limb paralysis is severe while the ophthalmoplegia is slight." Fisher thought that Collier's Group 1 contained cases similar to those he described as exemplifying a syndrome. Collier did not describe his individual cases.

The occurrence of albuminocytologic dissociation is important in diagnosis of the Guillain-Barré syndrome, but one should remember its variability. In the typical instance there is no increase in cells in the spinal fluid, but a slight pleocytosis (10 to 100 cells) occurs in approximately 20% of cases, according to Merritt.[2] Merritt also states than an increase in protein content is the rule but that values below 75 mg. per 100 cc. are present at the onset in 39% of cases. In Haymaker and Kernohan's[3] series, 20% of 50 autopsy-proven cases had spinal fluid protein values within normal limits, and in Baker's[6] series the spinal fluid protein was normal in 21% of 28 cases. The protein may be elevated initially and fall in the course of the disease. More commonly, it is normal early; a rise is detected only if sought for late. Changes in the colloidal gold reaction of the midzone or, rarely, of the first zone type may be associated with the increased protein content. This was noted in our first case.

Fisher considered the cases he described to be related to acute idiopathic polyneuritis, or the Guillain-Barré syndrome. Similarities are antecedent upper respiratory infection; rapid development of neurologic signs at onset; occurrence of facial diplegia, dysphagia, and dysarthria; presence of paresthesiae without significant sensory loss; rapid clinical improvement, and similar laboratory findings, including albuminocytologic dissociation. Dissimilarities are the absence of massive motor paralysis and lack of involvement of the lower extremities or proximal muscles. Fisher remarked that his cases had features which suggested central involvement of the nervous system rather than the peripheral findings usually noted in infectious polyneuritis. Symmetry of the external ophthalmoplegia with relative sparing downward gaze and the occurrence of cerebellar ataxia are rare in infectious polyneuritis. Elevation of the spinal fluid protein was detected in only one of Fisher's three cases. The progression of the cerebrospinal fluid changes in that patient are of interest: On the 3rd day one lymphocyte per cubic millimeter and a protein value of 36 mg. per 100 cc. were found; on the 5th day five lymphocytes, eight erythrocytes, and a protein value of 68 mg., and on the 30th day a crystal-clear fluid containing 348 mg. of protein per 100 cc. was noted. The demonstration of progressive albuminocytologic dissociation of mild but definite degree in our two cases tends to corroborate the suggested relationship of this clinical picture with the Guillain-Barré syndrome. However, it is important to realize that this may be a very delayed finding.

Although the Guillain-Barré syndrome was formerly considered clinically benign, the mortality rate in more recent series has varied between 15% and 60%.[2] Death is usually due to respiratory failure or intercurrent infection. Slow recovery is usual and residuals are infrequent.

The differential diagnosis of total external ophthalmoplegia of sudden onset is of particular interest. The onset of a myasthenic crisis after an antecedent upper respiratory infection must be excluded by testing with neostigmine or some such substance. A lack of mental changes, as confusion or stupor, distinguishes the cases under consideration from cases of the ophthalmoplegia and ataxia of Wernicke's disease. With the latter there is a history of malnutrition or alcoholism as well. Hemorrhage into a pituitary adenoma is likely to be associated with pronounced diminution in visual acuity and is accompanied by severe headache. A brain stem vascular accident producing total external ophthalmoplegia would profoundly affect consciousness by associated damage to the reticular formation. Basilar artery thrombosis causing ocular palsies would produce long motor and sensory tract signs. Other entities, such as bulbar poliomyelitis and neuromyelitis optica, are mentioned. Diphtheria, botulism, and exogenous toxins can be differentiated. The association of infectious mononucleosis with the Guillain-Barré syndrome should be kept in mind, and blood smears and heterophile agglutinins should be studied.

Summary

Fisher's report of external ophthalmoplegia, marked ataxia, and generalized areflexia occurring as an acute neurologic illness related to acute idiopathic polyneuritis (or the Guillain-Barré syndrome) prompted this discussion of two additional cases. On the basis of Fisher's three cases and our two cases, the syndrome has the following features: (1) all five patients were men, from 38 to 63 years of age; (2) antecedent upper respiratory infection; (3) external ophthalmoplegia—this tends to be total, but downward gaze may be spared; (4) retention of pupillary reflexes; (5) the presence of diplopia; (6) the occurrence of facial paralysis in three of the five cases (bilateral in two); (7) cerebellar ataxia; (8) generalized areflexia; (9) migratory paresthesiae, more prominent in trunk and upper extremities, in four of the five cases; (10) minimal or no sensory impairment; (11) absence of mental changes; (12) absence of motor weakness in the extremities; (13) albuminocytologic dissociation in three of the five cases; (14) recovery in from 7 to 12 weeks with no therapy.

Box 6, Johns Hopkins Hospital (5).

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Progression of Defects in Visual Fields Produced by Hyaline Bodies in Optic Disks

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The types of defects in the visual field produced by drusen in the optic papilla are well known.[1-3] However, only a paucity of references relate to the changes in the visual fields on succeeding examinations of patients having these hyaline masses.[4] We wish to report on 14 cases encountered at the Mayo Clinic in which one or more examinations of the visual fields were conducted at periods of 6 months to 24 years after the initial examination.

Report of Cases

CASE 1.—A 46-year-old woman registered at the clinic in 1925 with the complaint of headaches. Evaluation in the Section of Ophthalmology failed to uncover any ocular cause for the headaches. She related that the left eye always had been "poor" and that during childhood "it turned in." Visual acuity, with correction, was 20/200 with the right eye and 20/400 with the left eye. Hyperopia and astigmatism measured several diopters. Visual fields seemed full by the confrontation method. Ophthalmoscopy revealed structurally full anomalous pale optic disks with colloid deposits, more numerous in the left than in the right disk. In addition, chronic hypertensive changes of moderate severity were present in the retinal arterioles and choroidal degeneration was evident in the macular areas in each eye, more marked on the left. The visual fields were not charted at that time. The headaches were thought to be migrainous.

In subsequent years the patient was registered in the Section of Neurology six different times for complaints referable to trigeminal neuralgia and vertigo. In September, 1953, her visual fields were charted and an irregular contraction was found (Fig. 1*a*).

Two and a quarter years later the patient returned for evaluation of persistent neurologic symptoms. She contended that there had been further loss in the side vision. Charting of the fields disclosed further loss in both eyes (Fig. 1*b*) due to a superior arcuate scotoma confined to the central part of the field of the right eye and a generalized contraction in the field of the left eye. The ocular tension was normal.

CASE 2.—A 43-year-old woman came to the Section of Ophthalmology in 1925 to obtain a replacement for a recently broken pair of glasses. External ocular examination and examination of the visual fields by the confrontation method did not show any abnormality. Ophthalmoscopy revealed the retinal arteries to be mildly contracted and the disks to be structurally full and pale, owing to deposits of colloid within them.

During the next 27 years the patient visited the clinic many times for hypertension and occasionally for epiphora. In 1927 the visual fields were charted for the first time. An incomplete inferior altitudinal anopsia of the field of the right eye was detected with the use of a 3 mm. white bead at a distance of 280 mm. The field of the left eye was slightly depressed.

In 1930 and 1937 reexaminations at the 330 mm. perimeter with a 3 mm. white

Received for publication Dec. 26, 1956.

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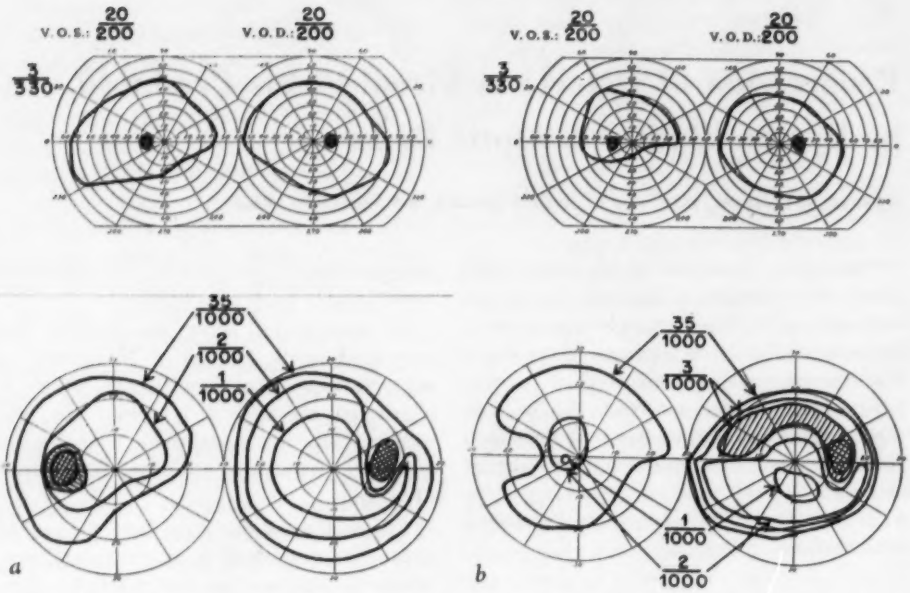
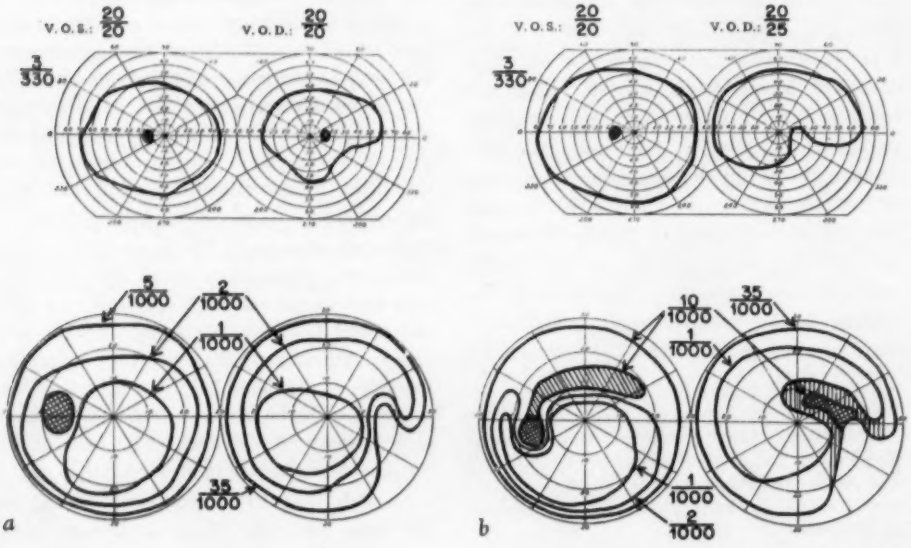


Fig. 1 (Case 1).—(*a*) Generalized contraction of visual field. (*b*) After two and one-quarter years.

target did not demonstrate further change. The first combined perimetric and tangent screen examination was recorded in 1942 and is chosen as a base line in presenting the visual fields in this case (Fig. 2*a*). A similar detailed record of the fields obtained in 1945 did not disclose significant change. The last complete charting, three years later (1948), demonstrated progressive loss in the visual field within the central 25-degree zone

Fig. 2 (Case 2).—(*a*) Contraction of visual field of right eye. (*b*) After six years.



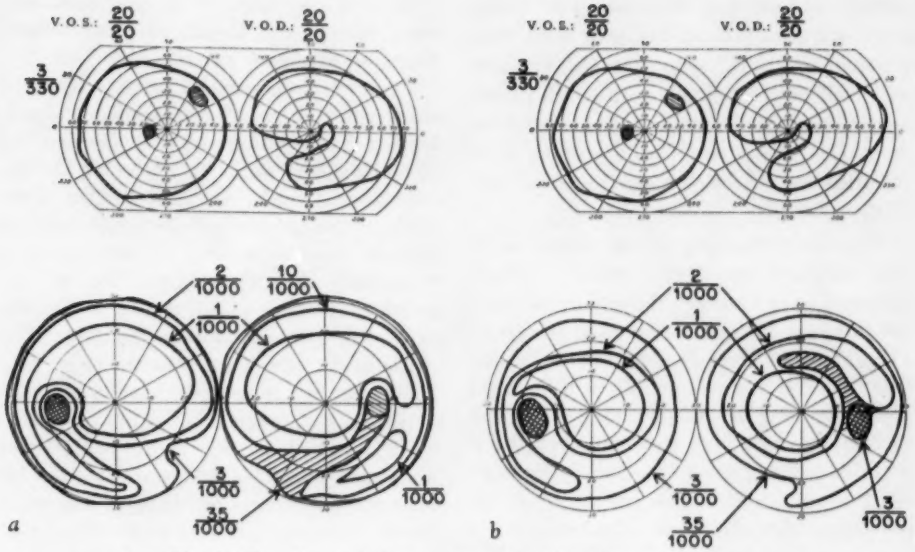


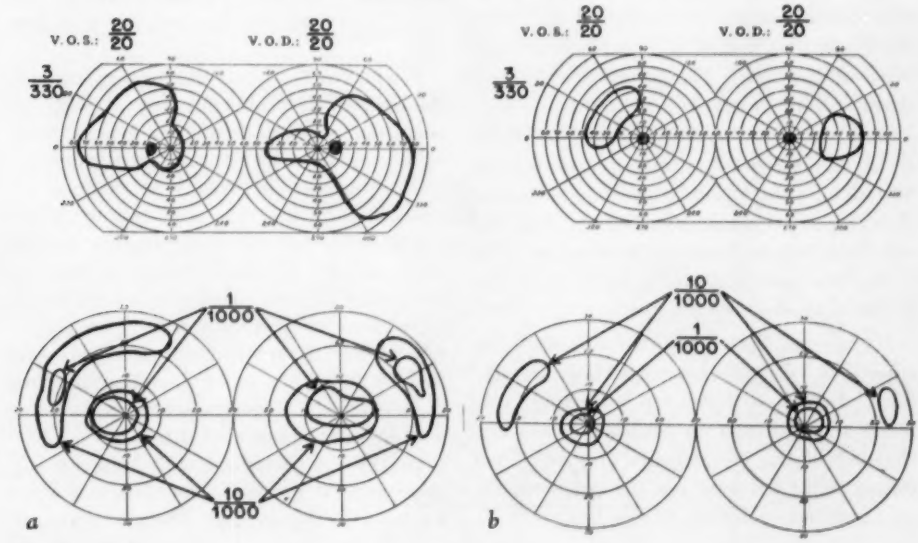
Fig. 3 (Case 3).—(*a*) Arcuate scotomas. (*b*) After seven years.

of each eye (Fig. 2*b*) in the form of superior arcuate scotomas.

In 1952 the patient died of a cerebral vascular accident and hypertension. Necropsy data were not obtained.

Case 3.—A 42-year-old man has visited the clinic 17 times between 1943 and the time of this writing, with symptoms referable to recurrent depression, tension, tension headaches, and chronic nervous exhaustion. He was sent to the Section of Ophthalmology initially in 1945 for evaluation of retinal blood vessels when his blood pressure was observed to be 150 mm. of mercury

Fig. 4 (Case 4).—(*a*) Nasal contraction with ring scotomas. (*b*) After eight years.



systolic and 90 mm. diastolic. The retinal arterioles were normal, but both disks were reported as "full," owing to the presence within them of hyaline masses which caused an elevation of the nasal half of the disks of 2 D. Visual fields at that time were recorded as full by the confrontation method.

The initial charting of the visual fields was obtained in 1949. Inferior arcuate scotomas were revealed, the one in the right eye breaking through to the nasal periphery (Fig. 3*a*). In 1956 charting of the visual fields showed progressive loss in the central 25-degree zone of each eye (Fig. 3*b*). The loss in the right eye took the form of a superior arcuate scotoma. The ocular tensions were normal. The patient made no complaints referable to the visual loss.

CASE 4.—A 37-year-old woman registered at the clinic in 1939, complaining of headaches. The results of examination of the eyes, including use of the confrontation method, were recorded as normal except for structurally full and pale disks due to colloid excrescences within them. No ocular cause for the headaches was found.

In 1942 the patient underwent simple mastectomy for benign disease, and while she was still under the effects of the anesthetic she fell out of bed and bumped her head on the floor. Thereafter she had frequent severe headaches preceded by brilliant scotomas. Charting of the visual fields (Fig. 4*a*) disclosed a binasal and inferior altitudinal contraction with ring scotomas. A series of roentgenograms of the skull did not show any evidence of abnormality. The headaches were considered to be of a migraine-tension type.

Eight years later, when she returned to the clinic for consultation regarding chronic heart disease, a follow-up evaluation was made of the drusen on the optic disks. Recharting of the visual fields (Fig. 4*b*) disclosed additional loss, but the patient made no complaints referable to this loss.

In 1952 she died of chronic rheumatic heart disease and associated renal failure. Necropsy data were not obtained.

CASE 5.—A 28-year-old farmer registered at the clinic in 1942 for evaluation of headaches. Examination in the Section of Ophthalmology failed to show any ocular cause for the headaches. Examination of the eyes, including use of the confrontation method, showed nothing abnormal except structurally full optic disks due to the presence of many colloid masses within the right disk and one within the left. The visual fields were nearly normal (Fig. 5*a*). The headaches were considered to be due to tension and fatigue.

He returned to the clinic 13½ years later, complaining of recurrent episodes of momentary dizziness on changing the position of his head. His eyes were reexamined and the visual fields were recharted (Fig. 5*b*). A definite constriction of the nasal part of the central field of the right eye was noted, as well as indefinite arcuate scotomas in the more peripheral field of that eye. The only other finding on complete general and neurologic examination was a position-changing (Type 2 of Nylén) nystagmus. Roentgenograms of the skull did not show evidence of any abnormality. A definite diagnosis could not be made, and he was urged to return for reevaluation at a later date.

CASE 6.—A 44-year-old woman came to the Section of Ophthalmology in 1933 for refraction while undergoing a general medical examination for chronic constipation and osteoarthritis. The results of external examination of the eyes and testing of the visual fields by the confrontation method were normal. Ophthalmoscopy revealed innumerable hyaline masses imbedded in the entire area of both optic disks. Because of this finding, the perimetric visual fields were charted (Fig. 6), and a binasal contraction was disclosed. A tangent screen examination was not carried out at that time.

In 1947 she returned with regard to the same general medical symptoms and again was seen in this section. The appearance of

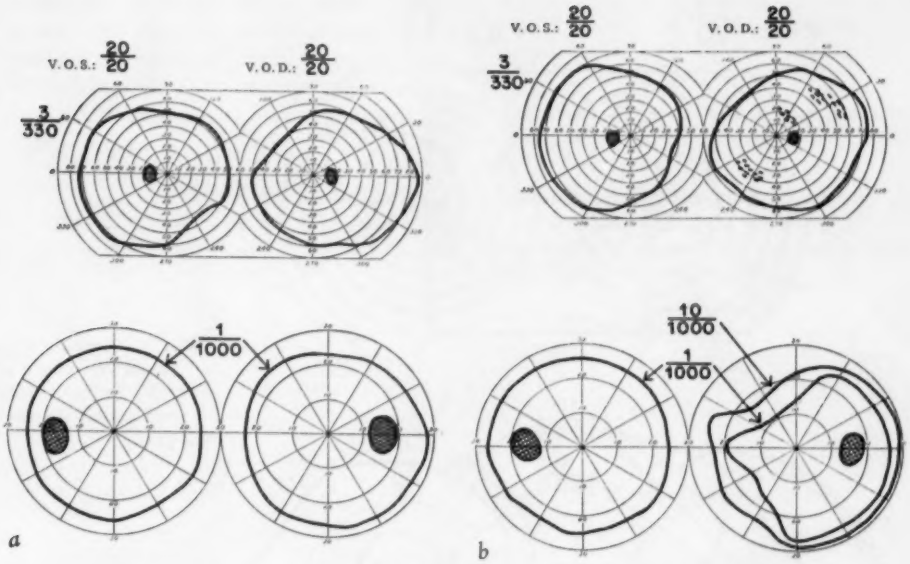


Fig. 5 (Case 5).—(*a*) Essentially normal visual fields. (*b*) After 14 years.

drusen on the disks had not changed, and there were no complaints referable to further visual loss. Charting of the visual fields disclosed further shrinkage of the isopters (Fig. 7) in the manner of an inferior altitudinal contraction of the field of the right eye and arcuate ring scotomas breaking through to the nasal periphery in the field of the left eye. On a visit in 1956 significant changes in the visual fields from those recorded nine years previously had not occurred.

The conditions of the other eight patients in this group of 14 were followed for periods which ranged from 6 months to 13 years (6 months, 6 months, 3, 4, 5, 7, 9, 13 years). The ages of the patients ranged from 14 to 79 years at the time of the initial examination. In two cases the visual fields were normal at all examinations. The condition of one patient was followed for 3 years; that of the other, for 13 years. In the other six cases the defects found at the first examination did not change during the periods of observation.

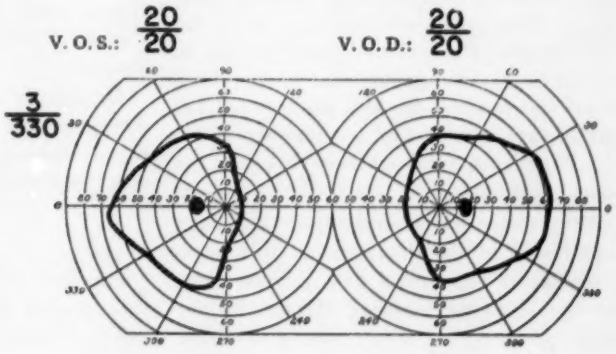


Fig. 6 (Case 6).—Binasal contraction.

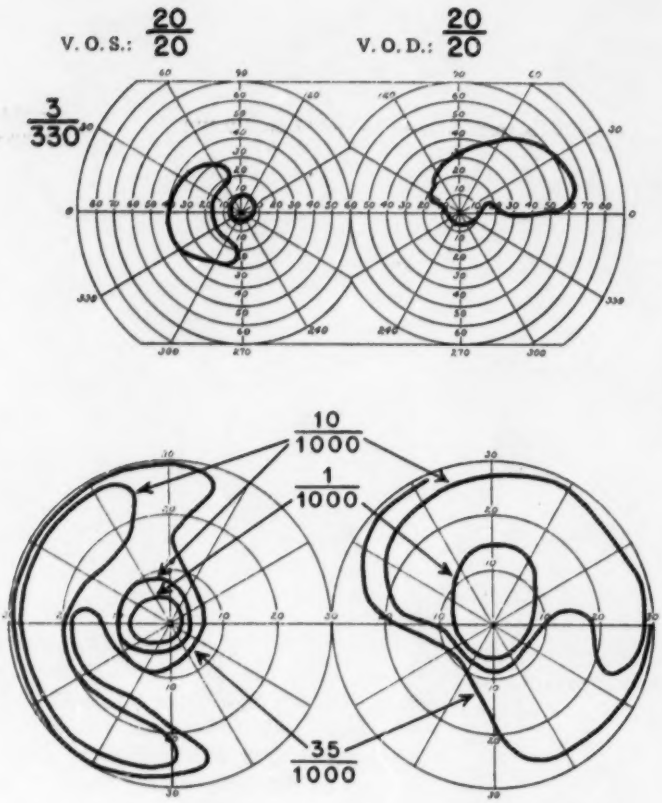


Fig. 7.—Same case as in Figure 6 after 15 years. No further change occurred during the next nine years.

Comment

Our records indicate that perimetric fields have been charted in 80 cases of hyaline masses in the optic nerve heads. In 14 of these more than one examination was conducted, with intervals of 6 months to 24 years between the initial and later examinations. This group comprises the basis for this report. The minimal time interval to elapse before change occurred in the visual fields was two and one-half years (Case 1); the average time interval was nine years. Of the 14 patients, 8 did not show change in the visual field during the period of observation.

Progressive defects in the visual field were manifested in the development of arcuate scotomas in the central field in four eyes, arcuate scotomas breaking through to the nasal periphery in four eyes, generalized contraction in two instances, and nasal contraction in one. We have not seen a single patient who has become blind by reason of drusen. The majority of patients appear to tolerate and adjust to the visual field loss, and few of them make complaints referable to it. In most instances any diminution in central acuity can be attributed to an uncorrected refractive error rather than to drusen.

In none of the 14 cases were significant changes in the ophthalmoscopic appearances of the drusen noted during the intervals concerned in this study.

Summary

Fourteen cases of hyaline masses in the optic papilla are reported in which one or more examinations of the visual fields were

conducted at periods of 6 months to 24 years after the initial examination. In six patients a progressive loss in the visual fields occurred during the periods of observation; in eight, no change was demonstrated.

Mayo Clinic.

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A Preliminary Investigation of Retinal Locus as a Factor in Fusion

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Since Burian [1] demonstrated that images falling on peripheral portions of the retinae could elicit fusional movements, some interest has been generated in this subject. The value of such a mechanism to the orthoptist has been suggested by a number of investigations [2,3,6] of fusional movements in patients having small angles of tropia. If techniques that utilize peripheral fusion are to be applied, it is desirable that its parameters be studied in the normal subject. This investigation represents an attempt to initiate a study of the parameter of retinal locus.

Burian [1] was able to demonstrate that peripheral fusion stimuli could cause disruption of central fusion. Winkelman [7] used this phenomenon in his studies on peripheral fusion. Lyle and Foley [3] were also able to show this, but they were unable to elicit central diplopia in the majority of their 50 subjects and found it to be transient in those experiencing it. These studies indicate that the peripheral fusion mechanism may, in some persons, take precedence over the central fusion mechanism. In order to study this, a comparison of the ability of equivalent central and paracentral targets to stimulate fusional movements was undertaken.

Winkelman [7] demonstrated that the intensity of peripheral fusion increases with larger peripheral targets. Lyle and Foley [3] showed that peripheral fusion was first noticed at 9, 12, and 15 degrees with squares subtending 2.5, 5, and 10 degrees, respectively. While target size is important in both studies, it should be pointed out that as it increases the retinal locus stimulated changes. The question, therefore, arises as to the relative fusion value of the area of the images as compared with their loci. This study will attempt to begin to answer this question.

Received for publication Jan. 15, 1957.

Dr. G. M. Breinin originally inspired this project and made it possible.

Apparatus

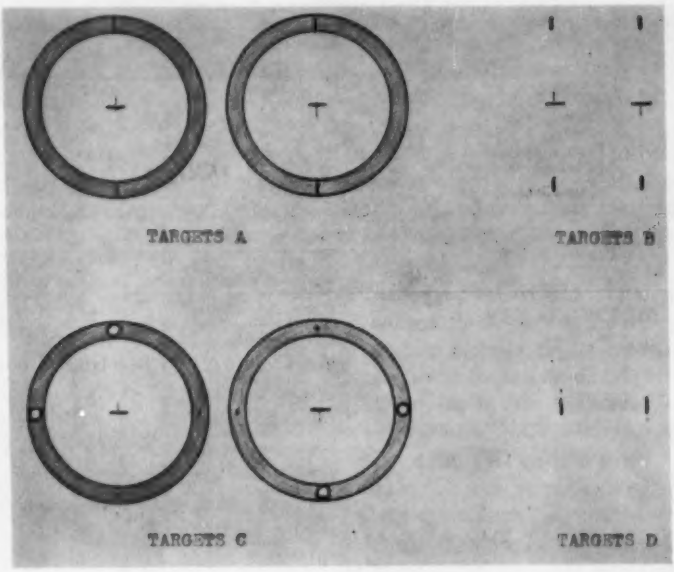
Apparatus consisted of an American Optical Company Wottring Troposcope and the following targets:

Targets A consisted of a red ring seen by the right eye and a green ring seen by the left. The inner limits of the rings were 5 degrees 6 minutes and the outer limits were 6 degrees 20 minutes from the fixation point. The rings were outlined in black India ink. In the vertical meridians, black India ink lines extended from the inner to the outer ring boundaries. In the center of each ring was a fixation target consisting of a 5 mm. horizontal black line from the midpoint of which extended a red or green 3 mm. vertical line in such a manner that when the targets were fused a central cross having a vertical limb that was half red and half green was seen.

Targets B were the same as Targets A without the colored rings.

Targets C represented a set of control targets which were the same as Targets A except that, instead of lines between the inner and outer boundaries of the rings, each ring contained two black dots and two circles positioned so that when the targets were fused a black dot was seen in each circle at 12, 9, 6, and 3 o'clock on the ring. The circles were 3 mm. in diameter.

Targets D consisted of centrally placed 4 mm. long vertical lines; one had a red dot above it; the other had a green dot below it.



Subjects

The 12 subjects were medical students and patients hospitalized for reasons other than ocular pathology. All had normal binocular vision and a corrected visual acuity of not less than 20/30 in the poorer eye. The age range was from 24 to 67 years.

Procedure

All measurements were made with the subjects wearing their distance corrections. The illumination was adjusted so that both targets appeared equally bright. The eyepiece separation of the troposcope was adjusted to correspond with the subject's interpupillary separation (P.D.), and the subjects were positioned so that their anterior corneal surfaces were 2.5 cm. from the eyepieces.

Vertical phorias were measured, and the instrument was adjusted to correct for them. Lateral phorias were measured and recorded.

The targets were presented at the zero position of the troposcope arms or, if fusion was impossible there, at the phoric position. The subject was instructed to look at the central fixation targets during all observations, and his eyes were constantly observed to assure that no attempts were made to look at the peripheral elements. As fixation disparity occurred, he was instructed to look midway between the red and green limbs of the cross. After orientation as to the components of the target, the subject was given a training period until he appeared to understand the judgements to be made. Since divergence is less subject to voluntary control than convergence, measurements were made only for this function. The troposcope arms were diverged until diplopia for the elements being tested was reported. This value was recorded as the break, and the troposcope arms were further diverged before being converged until fusion recurred. This value was recorded as the recovery. In order to eliminate practice and fatigue effects, the order of presentation was varied from subject to subject and in any one subject each judgement was made twice and then the order was reversed. Thus, four measurements were recorded for each subject for each element tested, and the results were averaged.

Fusion Limits for Target Elements

Target	Element	Break, Prism Diopters		Recovery, Prism Diopters,
		Mean	S. D.	Mean
A	Rings	7.9	3.4	2.4
C	Rings	7.3	3.8	2.5
A	Paracentral lines	6.0	3.4	2.2
B	Paracentral lines	6.1	3.2	2.1
D	Central lines	4.4	2.4	2.1

Results

The values in the Table were arrived at by calculating the mean for all determinations on the given target element and, in the case of the break values, determining the respective standard deviations. The groupings are determined by break values between which there was no significant difference. The significance of the difference between the break values of separate groups, as determined for correlated means, satisfied the criteria for better than the 0.05 level of confidence.

The recovery values are strikingly similar.

Comment

The good agreement of the average recovery values suggests that they were independent of the target used. One might postulate that the recovery of fusion is dependent on the stimulation of corresponding Panum's areas. Since the difference between the horizontal diameters of Panum's areas for the retinal loci investigated is on the order of several minutes of arc, a more sensitive experimental set-up would be required to pick up any differences that may have existed.

If upon relinquishing fusion the eyes assumed a phoric position and if, according to Ogle,[5] Panum's area is on the order of 10 minutes in horizontal diameter in the retinal region with which this study was concerned, one would have expected fusion to have recurred within 1Δ of the phoric position. This was not the case. Clinically it is rarely the case. The explanation for this apparent discrepancy is that the eyes do not assume the phoric position after performing vergence movements to the point of disruption of fusion, but assume a position that is close to that at which recovery occurs. This was demonstrated by determining "phorias" immediately after the break occurred in two trained observers.

The differences between the break values for central and paracentral targets may have been due to differences in visual acuity. The visual acuity at 5.8 degrees from the fovea has been given as 0.1 by Luckiesh and Moss.[4] If the minimum separable at the fovea is on the order of 30 seconds of arc, that at 5 degrees would be on the order of 5 minutes of arc. Even if the older 1 minute value of central minimum separable were used, a paracentral value of only 10 minutes of arc would exist. This hardly explains the 1.5Δ (51.6 minutes of arc) difference between the break values of paracentral lines in Targets B and the central lines in Targets D. It is probably safe to say that the paramacula targets represent a greater fusion stimulus. This could best be demonstrated by using techniques capable of objectively measuring eye movements made in response to central and peripheral stimuli.

The difference between Targets A and B existed in the smaller area of stimulus in Target B. One would expect that, if the area of the retinal image were an important factor in determining the ability of a target to stimulate fusion, the paracentral lines in Target A would have been seen double at a significantly higher value than those in Target B. Since this was not the case, it is suggested that peripheral fusion may be more dependant on the retinal locus of the fusion stimulus than on the total retinal area stimulated. This should be investigated for other peripheral loci by using projected targets.

If the area of the stimulus is not an important factor, one would not have expected the break values for the rings to be significantly different from those for the peripheral lines. The difference that existed may have been an artefact. The lines were more discrete. If the rings were not reported as double until adjacent contours were no longer overlapped, one would expect a difference equal to the thickness of the rings less that of the lines. This is about 2Δ and agrees well with the experimental results.

It should be pointed out that any conclusions drawn from this study are tentative. The troposcope is far from an ideal experimental instrument. It does not permit very fine adjustments or the use of more peripheral retinal loci. The instrument tubes themselves may influence fusion. This study does indicate that more elaborate experiments might yield worthwhile information.

Summary and Conclusion

A study of the ability of macula and paramacula targets to stimulate divergent fusional movements was undertaken. An attempt was made to determine the fusion value of retinal locus as compared with total retinal area stimulated. All measurements were made on normal subjects in a troposcope. The evidence suggests that (1) paramacula targets represent a greater stimulus to fusion than do central targets and (2) retinal locus rather than the area stimulated determines the effectiveness of peripheral fusion.

Further studies using projection techniques in which more peripheral targets may be utilized and conditions can be better controlled are indicated.

369 Frankel Blvd.

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Mydriatic Treatment of Shallow Chamber After Cataract Extraction

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Shallow anterior chamber occasionally is a sequel of cataract extraction. It is of two types. In one, the chamber simply does not reform after operation and a gross leak of aqueous generally can be demonstrated. In the other, commoner type, the anterior chamber does reform, but it decreases in volume a few days or even two to three weeks after operation. This report primarily concerns the second type.

The clinical picture is usually described as a triad of findings, consisting of shallow anterior chamber, hypotony, and choroidal detachment; however, this picture is not constant. The choroidal detachment usually antedates and outlasts the shallow chamber. In fact, a large choroidal detachment may develop without detectable alteration of the anterior segment. The shallow anterior chamber usually deepens spontaneously within a few days, but it may persist for weeks. Its persistence is considered significant because it favors the formation of anterior synechiae and secondary glaucoma.

Several explanations of postoperative shallow chamber have been proposed. A leaking wound cannot be detected in many cases, but the most widely accepted view is that a wound leak is the major causative factor. Bellows and his associates [1] believe that a wound leak produces an abnormal pressure relationship between the anterior and posterior segments. This is in turn followed, first, by obstruction of aqueous flow, vitreous block with edema, and congestion of the ciliary body and, later, by decreased aqueous production and subchoroidal transudation.

Chandler [2] has been of the opinion that a wound leak always is present, even though it may not be clinically demonstrated. He regards the choroidal detachment as a development secondary to the hypotony, because the latter favors transudation into the choroidal space.

Dunnington [3] also has expressed the belief that a wound leak is invariably present and has pointed out that aqueous can seep through a cataract wound without actual disruption. Then there are continued seepage, a boggy flap, and decreased volume of the anterior chamber.

In contrast, Reese [5] has found no proof that a leaking wound always underlies a shallow chamber. He suggests that removal of the lens may thin and weaken the face of the vitreous and predispose it to ectasia. This is followed by increased vitreous volume and advancement forward of the vitreous, with posterior detachment.

Still another view is that of Villaseca.[6] In his opinion, the anterior chamber is emptied by expulsion of aqueous through its normal channels, with resultant forward displacement of iris and vitreous. He attributes the choroidal detachment to traction by the base of the vitreous. Like Bellows and Reese, he postulates a turgescence of the vitreous which causes its increased volume.

With such a divergence of views relative to pathogenesis, it is to be expected that there also will be divergence of opinion relative to management. Kronfeld [4] thinks mydriatics are useful only in the eyes presenting a definite vitreous block, but in

Received for publication Dec. 26, 1956.

From the Department of Ophthalmology of the University of Oregon Medical School.

Presented before the Oregon Ophthalmological Alumni Association, Portland, Ore., September, 1956.

these he usually finds the intraocular pressure to be elevated. Like most other authors, Kronfeld [4] recommends surgical intervention if a definite wound leak is noted. When a leak is not present, miotics, in his experience, are the only therapeutic measures that have been consistently effective.

Reese [5] also advocates the use of miotics for shallow chamber following round pupil extraction. He puts the patient to bed, dilates the pupil with 10% phenylephrine (Neo-Synephrine) hydrochloride to let the vitreous drop back, and then reconstricts the pupil with a miotic. He considers a contracted pupil to be desirable following surgery because the iris diaphragm gives support to the hyaloid. In patients developing shallow chambers after surgery, he has reconstructed the chamber with isoflurophate in five hours.

Villaseca [6] is in agreement with Reese [5] relative to the use of miotics. He advises that mydriatics should be avoided postoperatively, and, if used at all, they should be of the short-acting type and should be alternated with miotics. Villaseca [6] routinely uses air in the anterior chamber after operation to keep the vitreous back until the chamber re-forms.

There seems to be a definite preference for conservatism and for medical over surgical treatment. The natural course of shallow chamber is toward spontaneous reformation; consequently, it is difficult to evaluate any treatment. In 500 consecutive cataract extractions, reported by Kronfeld [4] from the Cook County Hospital, late flat anterior chamber occurred in 27. It was commoner in eyes subjected to peripheral iridectomies than in those in which complete iridectomies had been done. Spontaneous re-formation occurred in 25 of the 27 eyes.

There is agreement regarding such prophylactic measures as watertight closure of the wound, accurately placed sutures (not too deep), good postoperative iris position, and avoidance of external pressure on the globe. Increased intraocular instrumentation and excessive manipulation at the time of operation should also be avoided.

At the University of Oregon Medical School our experience confirms the observation that failure of the chamber to re-form after operation invariably is due to inadequate closure of the incision. In the last 200 consecutive cataract operations, performed by the resident staff, the anterior chamber had re-formed without exception by the time of the first dressing, 24 hours postoperatively.

At our institution, delayed re-formation of the chamber seems to have been completely eliminated by the use of mild chromic absorbable surgical (gut) sutures which are covered by a limbus-based flap, 4 to 5 mm. wide, of both Tenon's capsule and conjunctiva. In contrast, late decrease in volume of a previously formed anterior chamber, choroidal detachment, and hypotony have not been eliminated by this technique.

In our series of 200 consecutive cataract extractions there were 14 eyes with delayed loss of the anterior chamber, an incidence about equal to that in the series reported by Kronfeld.[4] This in itself suggests a different pathogenesis for the two types of postoperative shallow chamber.

The earliest onset of delayed loss of the anterior chamber in our series was the fourth postoperative day. The latest onset of this complication was the 21st postoperative day. In the majority of the eyes, the shallow chamber was noted during the second postoperative week.

There were several other noteworthy findings in our series. A possible external leak in the wound was demonstrated in only 1 of the 14 eyes. In five other eyes a filtration bleb was evident at one time or another. In the remaining eight eyes there was no evidence of a leak from the anterior chamber under the flap or externally. In this respect, our observations are similar to those of Reese [5] and Villaseca [6]; that is, a minority of eyes have a leaking limbic wound.

Hypotony was present in all 14 eyes, but choroidal detachment was present in only 10. In most of the eyes choroidal detachment was noted prior to the onset of the shallow

chamber and it lasted several days to two weeks after re-formation of the chamber.

Choroidal detachment also was observed to occur without alteration in the volume of the anterior chamber. This occurred in 17 of the remaining 186 eyes operated on. In all 17 hypotony was present. This combination of findings suggests that choroidal detachment is primarily associated with hypotony; however, this interrelationship requires additional studies. For example, there is a possibility that a choroidal and ciliary body detachment of considerable magnitude might favor forward displacement of the vitreous. Also, ciliary body detachment might appreciably reduce formation of the aqueous. There is evidence that this does occur. In any event, gross choroidal and ciliary body detachment is not a constant part of the clinical picture of shallow anterior chamber and may occur independently.

The most significant finding in our 14 eyes with loss of the anterior chamber was evidence of obstruction to the flow of aqueous from the posterior to the anterior chamber. Each of the 14 eyes showed increased convexity of the peripheral iris plus herniation of vitreous both into the pupillary area and into the area of iridectomy. In several patients there were frank adhesions of the pigmented epithelium to the vitreous face; however, the response of these eyes to intensive mydriatic therapy has provided the most dramatic evidence that obstruction in the primary circulation plays a role in the persistence of the shallow anterior chamber.

In one of Reese's patients, the chamber re-formed in five to six hours with isoflurophate. This is the earliest re-formation time that has been reported. In contrast, we have repeatedly observed pronounced deepening of the anterior chamber, flattening of the iris, and reduction of the vitreous herniation within 30 to 90 minutes after the onset of extreme mydriasis. It should be emphasized that a moderate amount of mydriasis, such as that induced by atropine alone, is not sufficient in most cases to open the pupillary block. It is essential that the pupil be so dilated that a communication is reestablished between the anterior and posterior chambers. This means inducing complete paralysis of the iris sphincter by such drugs as scopolamine or atropine and stimulating the iris dilator by sympathomimetic drugs. One of the most suitable combinations is cocaine with either 1% epinephrine or 10% phenylephrine.

In our series, anterior chambers of several eyes re-formed during the period of extreme mydriasis but became shallow again when the pupil constricted or was only moderately dilated. Invariably, the chamber re-formed again with extreme mydriasis. In one patient the anterior chamber became shallow on four different occasions over a 10-day period and each time was restored within 1 to 2 hours by the creation of extreme dilatation. After the fourth restoration the chamber remained deep. We have observed no such response with the administration of a miotic, and such response has not been reported by others. In none of the eyes in our series was it necessary to resort to posterior sclerotomy or anterior chamber injections of air. We have not observed the benefit with acetazoleamide (Diamox) reported by others. Our past experience with miotics is similar to that reported by other authors. A few patients were made worse, and a few seemed to improve, possibly because the miosis may have broken free adhesions of the iris to the vitreous. In no case was a dramatic re-formation of the chamber observed as with intensive mydriatic treatment.

If it is correct that a pupillary block is a major factor in decreased volume of the anterior chamber, it should be feasible to reduce the incidence of this complication by performing an adequate iridectomy and maintaining good mydriasis throughout the first postoperative weeks. We are now using mydriatic and cycloplegic drugs and avoiding miotics during this period, but it will be some time before the series is large enough to be statistically significant.

Conclusions

In presenting this review and interpretations of our own clinical experience, we realize there are still unanswered questions about shallowing of the anterior chamber, hypotony, and choroidal detachment developing in some patients several days or even weeks after cataract extraction; however, in presenting evidence that the pupillary block is an additional part of the entity, we are providing a rational basis for effective treatment. In the absence of a detectable wound leak, this treatment consists of inducing and maintaining extreme mydriasis. Moderate mydriasis may not keep the pupil from adhering to the vitreous face. It is this adherence which blocks aqueous flow from the posterior into the anterior chamber. The occasional success with miotic therapy observed by us and reported by others might well be due to rupture of posterior iris adhesions induced by contraction of the iris sphincter, but, even then, re-formation of the anterior chamber is slower and less dramatic than with extreme mydriasis.

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Nonspecific Granuloma of Lacrimal Sac Harboring Polyethylene Tube

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Nonspecific granulomas of the lacrimal sac are not common, and so far only 26 cases have been reported in the literature (Duke-Elder [1]). They develop in chronic dacryocystitis as polypoid formations or they follow accidental injury, from probing and as a reaction to retained foreign bodies in the sac.

The case to be reported here is of interest because the granuloma developed after a polyethylene tube had been inserted in a stenosed lacrimal sac to effect lacrimal drainage.

A 79-year-old white woman was first seen September, 1955, because of a painful swelling in the region below the inner corner of the left eye. She gave a history of epiphora and purulent discharge from the right lacrimal sac three years previously, and the sac had been removed one year later. At that time, epiphora commenced in the left eye, and a polyethylene tube was inserted into the lacrimal pathways. This did not relieve her symptoms; instead, the watering got worse. A purulent discharge developed, and she noticed a swelling in the region of the left lacrimal sac which was painful. She was then treated with penicillin injections, which did not improve this condition.

In the previous few months the swelling and her discomfort had increased.

In the region of the left lacrimal sac the skin was bluish-red and a walnut-sized well-defined tumefaction of elastic consistency could be palpated. On massage of this mass no fluid escaped from the lacrimal puncta, and this manipulation was very painful. The lacrimal puncta and the canaliculi were normal, and except for a chronic conjunctivitis the eye was normal too. The preauricular node and the submaxillary nodes were not palpable. The sac could not be irrigated. A probe could be passed through the canaliculi, but a firm resistance was felt at its entrance into the lacrimal sac. A lacrimal canule on an empty syringe was introduced into the canaliculus, and a droplet of sanguineous fluid was obtained by aspiration. Two days of treatment with antibiotics resulted in some relief of pain, but no objective change was noted. Inspection of the nose with a speculum showed the end of a polyethylene tube in the middle meatus.

The diagnosis was chronic dacryocystitis and tumor of the lacrimal sac containing a polyethylene tube.

On Sept. 27, 1955, a dacryocystectomy was done with use of local anesthesia. At dissection there were encountered firm adhesions of the sac on the lateral side. After the lower end of the sac (junction with the lacrimal duct) was severed, a polyethylene tube was cut and purulent fluid escaped from the sac. A 13 cm. piece of plastic tubing, 1 mm. in diameter, was recovered from the nasolacrimal duct and the nose. From the upper part of the sac at the point where the canaliculus had been severed the upper end of the polyethylene tube protruded for 1.5 mm. Its end was flaring and frayed. The appearance of the tubing at the lower end of the sac was similar. The diameter of the polyethylene tube protruding from the ends of the lacrimal sac was about 2 mm., because of swelling of its walls, but its lumen was unchanged. Recovery from surgery was uneventful.

Examination of the specimen. Gross findings: The lacrimal sac was reddish-blue,

Received for publication Dec. 26, 1956.

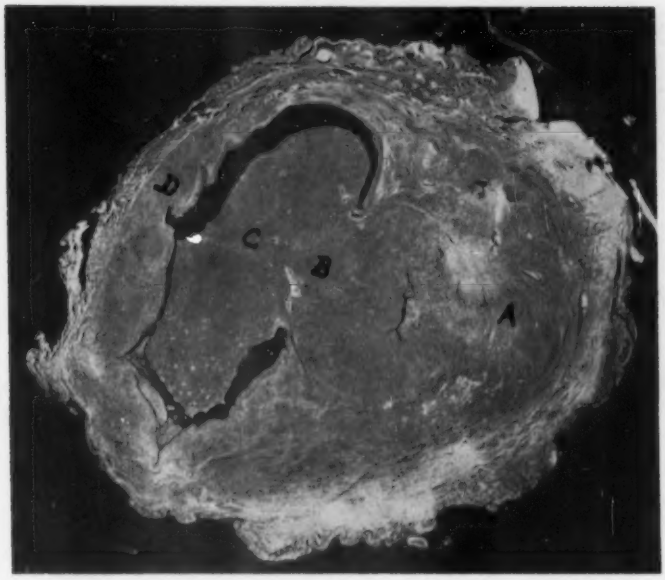


Fig. 1.—Photograph of microscopic slide of lacrimal sac with nonspecific granuloma. *A*, lateral wall with miliary abscesses; *B*, pedicle of granuloma; *C*, granuloma; *D*, medial wall. Reduced from mag. × 14.5.

2.25 cm. long, and 1.5 cm. in diameter, with the frayed and flaring ends of the plastic tube protruding 1.5 mm. from the upper part of the lateral wall (where the canaliculus had been cut) and at its lower end. The outside of the sac was smooth, except for a few bone spicules adhering below.

Microscopic findings: The transverse diameter of the lacrimal sac was 8 to 10 mm. The medial wall and the fundus of the sac were 0.7 to 1.1 mm. thick; its columnar epithelium was swollen, often raised to form small papillae, and showed widespread mucoid degeneration. The mucosa and the submucosa were thickened and diffusely infiltrated with small lymphocytes; cuffing of the deep submucosal vessels was widespread.

The greater part of the lateral wall was more than 4 mm. thick, and its columnar epithelium was thickened, with considerable mucoid degeneration. The mucosa and the submucosa were diffusely and densely infiltrated with small lymphocytes, plasma cells, numerous mononuclear cells, and small round foci of polymorphonuclear leukocytes with central necrosis. The blood vessels were very engorged and fresh, and old hemorrhages were seen between the inflammatory infiltrates (Figs. 1 and 2).

From the middle third of the lateral wall a mass protruded into the cavity of the lacrimal sac, nearly filling it. It was adherent to the wall by a 5 mm. broad and 2.25 mm. thick pedicle, in which large ves-

Fig. 2.—Photomicrograph. Medial wall of lacrimal sac, granuloma with miliary abscess (necrosis). Reduced from mag. × 22.

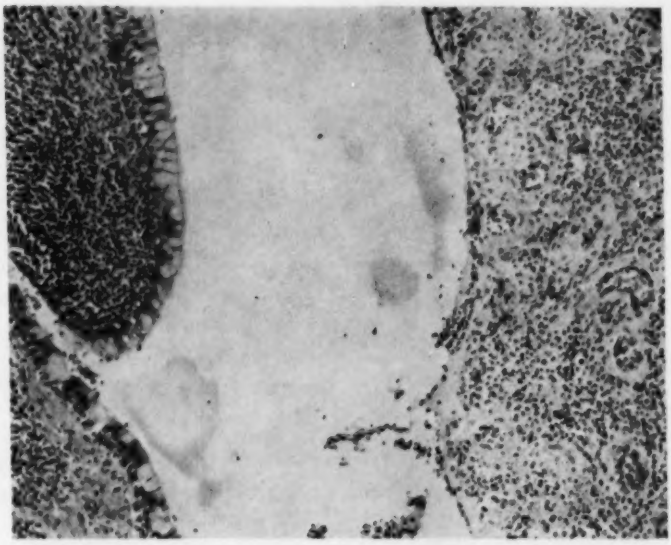
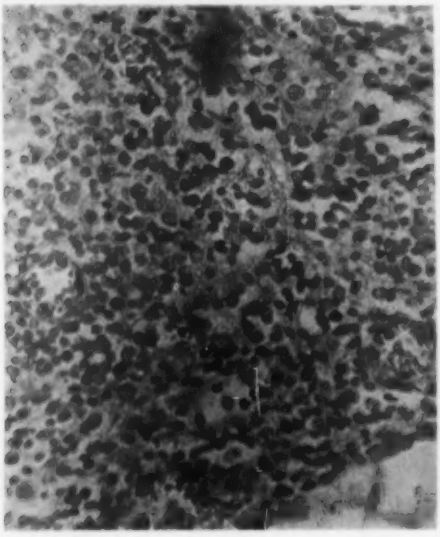


Fig. 3.—Photomicrograph. Mucoid degeneration of columnar epithelium of lacrimal sac and nonspecific granuloma, with free space between them. Reduced from mag. × 145.

sels were seen. Around the pedicle the epithelium of the lacrimal sac showed a squamous metaplasia. The mass was composed predominantly of plasma cells and scattered polymorphonuclear leukocytes; it was very rich in capillaries and endothelial cells, and in most slides small round accumulations of polymorphonuclear leukocytes with central necrosis were noted. A fine net of young connective tissue was present, as well as small fresh hemorrhages and blood pigment. No foreign body giant cells were noted. A few Russell bodies and large mononuclear cells containing a pinkish amorphous particulate matter were present. There was no epithelial covering of the granulomatous mass. In some areas polymorphonuclear leukocytes adhered to its surface; in others it was covered by a sheet of pink-staining amorphous substance. It averaged 5.5 mm. in diameter (Figs. 3 and 4). The narrow space between the mass and the medial wall was partly empty, or it contained some fibrin with polymorphonuclear leukocytes, as well as pink-staining amorphous particles in the form of rings and ovals, most numerous near the pedicle. It was noted that the granuloma above and below the pedicle was bulging, mushroom-like, into the enlarged cavity of the sac.

Fig. 4.—Photomicrograph. Nonspecific granuloma, with plasma cells, mononuclear cells, capillaries, and endothelial cells and capillaries. Reduced from mag. × 400.



The course of the plastic tubing within the lacrimal sac could not be established from the microscopic slides. There was a narrow free space between the mass and the medial wall, which in some areas was narrower than the diameter of the tubing, but

as purulent exudate escaped from the sac after its lower end was cut the spatial conditions existing before surgery were altered.

The pathological diagnosis was chronic dacryocystitis with miliary abscesses and nonspecific granuloma of the lacrimal sac.

It was perplexing not to see the polyethylene tube in the serial microscopic slides. Therefore, a piece of the plastic tube which had been removed at surgery from the nasolacrimal duct and the nose was fixed, embedded, and stained with the same technique as was used for the specimen of the lacrimal sac. On microscopic examination it was noted that the tubing had dissolved, and on the slide were seen only pink-staining amorphous residues.

The polyethylene tube had dissolved in the xylene used in preparing the slides, as xylene is one of the solvents of this plastic. Unfortunately, I had not been aware of this fact when the specimen was sent to the laboratory after surgery. The changes of the plastic tubing within the sac thus had escaped direct microscopic study.

Comment

A case of dacryostenosis had been treated by the insertion of a polyethylene tube of 1 mm. diameter to effect drainage of the tears. It had remained in the sac and nose for about two years. This procedure resulted in aggravation of the epiphora and formation of a painful swelling in the region of the lacrimal sac.

Polyethylene tubing was first used in the repair of stenosed and of lacerated lacrimal canaliculi by Henderson [2] and Callahan.[3] The tubing was left in the canaliculi up to 45 days, and the tissues were tolerant of this material. Veirs [4] extended the indication for this procedure to include stenosis of the nasolacrimal sac and left the tubing in place for one week. In a follow-up study Henderson [5] reported that the plastic tube had remained in the canaliculus for 139 days in one of his cases, and no significant irritation or visible foreign body reaction was noted. It seems noteworthy that he did dacryocystorhinostomies in the cases of stenosis of the canaliculi treated with polyethylene tubes; the plastic thus was not exposed to long-lasting stagnant secretions. Vicencio,[6] in a report on the results of treatment of the stenosed nasolacrimal duct with polyethylene tube, observed granulation tissue at the lower punctum in a case in which the plastic tube had remained in situ for 1 month and 14 days.

Gross alterations of the plastic tube protruding from the lacrimal sac were noted after its excision in the present case. These consisted of thickening of the wall to twice its former diameter and fraying and flaring of the cut ends. The lumen of the tubing was unchanged and not clogged.

How this nonspecific granuloma originated could not be determined from the microscopic slides. There was no definite foreign body reaction present in the wall of the sac or in the nonspecific granuloma itself. The presence of multiple microscopic abscesses amid the chronic inflammatory changes of the wall and granuloma is remarkable.

Changes in the polyethylene tube due to a slow process of solution of the plastic and absorption of water in the presence of body fluids, organic acids, and enzymes from the secretion of the blocked sac are to be considered.

The findings of the unchanged appearance of that part of the plastic tubing retained in the nose, in a milieu free of the above-mentioned noxious factors, lends support to this assumption.

Information from a research chemist (Lindsley [7]) on the effect of mucopurulent secretion on polyethylene was as follows: "Prolonged intimate contact with various body fluids at body temperature may show over very long periods of time an appreciable amount of solution, while ordinary laboratory tests might show no effect. And, of course, the presence of enzymes can complicate the picture." Bockhoff and Roth [8] write that the plastic is permeable in their sections by certain organic acids.

Thus, soluble substances derived from the plastic under the above-mentioned circumstances could have caused the unusual microscopic changes of the sac and the granuloma. This nonspecific granuloma differed further from others developing in chronic dacryocystitis in that it had no epithelial lining on its surface.

Summary

A nonspecific granuloma developed in a stenosed lacrimal sac two years after the insertion of a polyethylene tube. The lacrimal sac was excised, and the cut ends of the plastic tube appeared frayed and the wall twice as thick as the rest of the tube retrieved from the nasolacrimal duct and nasal cavity. Miliary abscesses were present in the wall of the sac and in the granuloma, but no foreign body giant cells were seen. The polyethylene tube in the sac was unintentionally dissolved when the slides were treated with xylene, one of its solvents. A slow process of solution of the plastic exposed to purulent secretion at body temperature, to organic acids, and to enzymes, over a very long period, is believed to have caused the granuloma.

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New Scissors for Cataract Extraction

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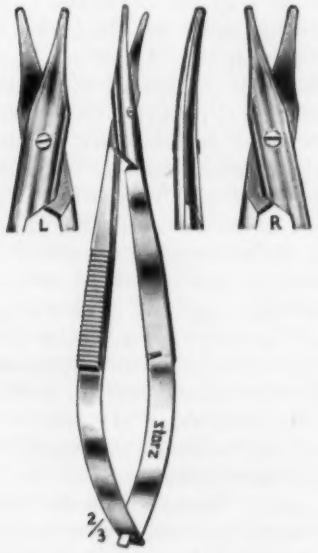
A scissors is described which has two features of advantage for enlarging corneal or limbal incisions in cataract extraction. First, it has an unusually heavy shank with short blades, patterned after a wirecutting scissors (Figure).* This design insures easy and clean cutting of corneal or corneoscleral tissues without springing of the blades and crushing of tissues, which is frequently encountered with the longer, more slender blades of many scissors. Secondly, the blades are wide, with rounded tips, which push the iris away from the cutting edges. Buttonholing of the iris, a not infrequent complication with the more conventional, slender blades, is thereby prevented. Although the blades may appear unnecessarily heavy and cumbersome to casual inspection, it must be remembered that only the terminal 4 to 6 mm. of a blade is inserted into the eye for cutting purposes. No disadvantage therefore accrues.



Corneoscleral scissors with heavy shank and blunt tip. Inset shows scissors for right and left limbus.

The scissors come in a set of two pairs, one for incising the right- and the other for the left-hand limbus, as viewed from above. The anterior blade is inserted into the anterior chamber, and thereby makes the incision further centrally in the cornea, in more avascular tissue, than if the posterior blade were within the eye. A spring handle facilitates handling and use of the instrument.

Received for publication March 19, 1957.

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* Manufactured by Storz Instrument Company, 4570 Audubon Ave., St. Louis 10.

Annual Reviews

Strabismus

Review of the Literature for 1956

MARSHALL M. PARKS, M.D., Washington, D. C.

The review of the 1956 literature dealing with strabismus was written with the dual purpose of (1) presenting new ideas and (2) submitting new facts that either support or contradict old concepts.

Basic Science Literature

Sensory.—One of the most thought-provoking and prevalent subjects in the literature this year concerns the theories of binocular vision.[1-3] It appears that there is accord on the important basic fact that a rigid, innate, anatomicophysiological correspondence exists between retinal receptor cells and occipital lobe cortical ganglion cells. This arrangement is vital to the explanation of integration of nondisparate similar retinal images into a fused perception by the corresponding ganglion cells. As attested to by Panum's fusional space, it is reasonable to assume there is a degree of elasticity in the ganglion-cell integrative system so that similar retinal images do not have to be rigidly nondisparate in order for a perception of fusion to be experienced.

The absence of integration occurring (1) for similar retinal images outside Panum's fusional space, as well as (2) for dissimilar retinal images within or without Panum's area, poses no problem. The former provokes diplopia, but the latter dilemma is solved by a second process of binocular vision, referred to as retinal rivalry.[1]

A third process inherent in the physiology of the corresponding ganglion cells which convert retinal images into perceptions is stereopsis.[1] On the basis of Ogle's (1952)[4] study, and subsequent reports in 1956,[5,6] it is apparent that stereopsis is possible even though the disparity of similar images is beyond the limits of Panum's fusional space. Consequently, fusion and stereopsis are recognized as separate components of the integrative process. These plus the phenomenon of retinal rivalry comprise the basic normal mechanisms of binocular vision, stereopsis and retinal rivalry being described as complimentary.[1]

Since, according to this concept, fusion and stereopsis are considered distinct entities, Worth's system of grading fusion is suggested to have outlived its usefulness.[7] Aside from this, it is interesting to note how well this concept [1] explains an observation of Hamburger's (1952)[8] that the highest grade of stereopsis was found among those with good binocular vision and lively retinal rivalry. Conversely, neither the rare case of horror fusionis nor the subject intoxicated with alcohol have single binocular vision. The image of each eye is simultaneously and independently perceived, while stereopsis and retinal rivalry are unable to be elicited.[1,9] Similarly, hypoxic conditions (high altitudes) quantitatively reduce the stereopsis perception in normal subjects and hyperoxic conditions improve low-grade stereopsis.[10] A sedative drug, bromdiethylacetyl urea (Adalin) has the same effect as hypoxia.[11]

Ogle [4] originally determined the limits of disparity that permit stereopsis to be in the magnitude of 20 minutes of arc in the macular area and nearly 4 degrees at the

Received for publication March 4, 1957.

peripheral angle of 6 arc degrees. One paper this year indicates that disparity up to about 7 degrees[12] permits qualitative (gross) depth localization. The quantitative depth perception test being a subjective analysis, it produces results in children in inverse proportion to the complexity of the test.[13]

Binocular magnification devices, similar to those worn by a surgeon, improve the depth discrimination, since the object can be viewed nearer with than without them and this increases relatively the interpupillary distance, hence enhancing the stereoscopic disparity.[14] Increasing the viewing distance reduces the part image disparity (stereopsis) plays in depth discrimination, and at 2000 ft. it is estimated that the threshold of stereopsis is exceeded.[15,16] Stereopsis, therefore, is of little value to automobile drivers and pilots. In fact, its total absence is so well compensated by monocular clues that it probably causes no more difficulty than deficient color discrimination in the commonplace vision of the afflicted person.[17]

Convergence has no effect on stereoscopic acuity.[18] Searching movements permit better stereoscopic acuity than when the eyes are in a completely static state.[1] Stereoscopic depth was reported by Verhoeff (1933)[19] to diminish as the illuminance of background of the target presented to one eye was lowered, but new studies deny this.[20] Stereoscopic depth from disparate images that were unequally illuminated remained stable as long as both images could be perceived. Stereopsis is present in the after-image, although fine details are lost, as are any of the fine pattern details in an after-image.[21]

The periphery of the retinas was described by Burian (1939)[22] to contribute significantly to fusion, and the same comment was later repeated.[23] A new idea was advanced to explain why peripheral fusion is achieved more easily than central fusion.[1] It was postulated that greater numbers of combined rods and cones in the periphery converge to a single cortical ganglion cell, and so cortical representation of the peripheral retinas is small compared with the extensive cortical area that represents the maculas. On the basis of the principle that the less the cortical disparity the easier the integration, it should follow that fusion of disparate images on the peripheral retina is more easily accomplished than integration of those more centrally located.

Motor.—Some significant observations and studies on the horizontal disjugate movements have been reported this year. Four types of convergence are claimed by Adler[24]; (1) voluntary, (2) tonic, (3) accommodational, and (4) fusional. Voluntary convergence results from impulses initiated in the frontal lobe. The source of impulses causing tonic convergence (a postural reflex) is unknown, but speculation is that such impulses govern the basic tonus of the subcortical convergence center. For some unexplained reason this basic tonus tends to be excessive in young children and infants. The accommodational and fusional convergences are components of the optomotor reflex.

Proof that an active divergence mechanism exists has been aided considerably by electromyographical demonstration of firing in the lateral recti during abduction.[24] It is implied that there is both (1) tonic and (2) fusional divergence. The tonic convergence and divergence police one another, and an imbalance could result in horizontal heterotropia, the direction of the visual axis being dependent upon which one is predominant.

Electromyographically,[25] the lateral rectus has been shown to contract early in convergence and the position of convergence is reached only by an oscillating process of medial rectus firing followed by lateral rectus firing, presumably to check the strong contraction of the medial rectus.

There is a difference in the behavior of the eyes when convergence and divergence amplitudes are measured.[26] As the convergence amplitude "break" point is neared, the pupils constrict and the palpebral

fissures narrow (enophthalmos). It is reasoned that at this point the fusional convergence amplitude has been reached and the patient begins to apply accommodative convergence. The divergence amplitude was lacking in any similar phenomenon, and between the "break" and "recovery" points the eyes remained rather statically diverged and recovered at about the "break" point. The convergence pattern was extremely variable and did not possess the repeatability of the divergence pattern. In convergence, after the "break" point there was great searching of convergence and divergence movements before "recovery" was again established. Also, it was noted that in neither convergence nor divergence measurements did the eyes immediately return to the zero phoria starting position. After convergence amplitudes, 0 to 2.4Δ of esophoria remained, as compared with 0 to 1.5Δ of exophoria after divergence determinations. Recovery to zero phoria took between 4 and 20 seconds after measurements were completed. Tani et al. think that there is an intraorbital displacement of the eyes nasally in convergence and temporally in divergence.

The responses of convergence and divergence to a 1.5 degree disparate stimulus are quite dissimilar.[27] The usual reaction time of 0.15 to 0.20 second is required before convergence movement occurs. The divergence reaction time is 0.175 to 0.225 second. The convergence movement is rapid and choppy, the 1.5 degrees of convergence being completed in 0.4 second from the time it starts. The divergence movement is very slow and smooth.

There is little similarity between a conjugate movement (horizontal) and a disjugate (convergence) movement in the time required to execute them.[27,28] The version (saccadic movement) is carried out at about 400 degrees per second, while the vergence is achieved in the range of 8 degrees per second. In asymmetric convergence, i. e., convergence on a point displaced from the straight-ahead position, saccadic movement aligns the eyes so that the near fixation point bisects the ultimate convergence angle. This is followed by simultaneous convergence of the foveas until fixation of the near point is established.[27] The difference in action time between saccadic and vergence horizontal movements has been attributed to the two histological types of motor endplates in the extraocular muscles. In fact, it is suggested that vergence movements are of the order of autonomic innervating system actions, since the velocities of movements of the intraocular muscles are so comparable.[28]

The ratio of the accommodative convergence to an accommodative stimulus change is markedly increased with homatropine.[29] A similar study with isoflurophate (DFP) shows just the reverse of these findings.[30] Instilling 0.2%, 0.1%, and 0.05% isoflurophate caused an increased amplitude of accommodation, which reached a plateau, with use of all concentrations, of 15 D.; this was reached in 30 minutes with use of the 0.2% solution and by 1 hour in the case of the 0.1% and 0.05% solutions. Accommodation declined to normal within 72 hours after instillation of the 0.2% and 0.1% solutions and by 36 hours in the case of the 0.05% solution.[31]

Many topics pertaining to the motor aspects of strabismus other than disjunctive eye movements have appeared in the literature, but each is rather unrelated to the others. For example, it was entirely a novel idea to study the uptake of radioactive phosphorus in the horizontal recti in strabismus.[32] Esotropia is characterized by the uptake of the medial rectus being greater than that of the lateral rectus. A new approach for the treatment of strabismus is opened by the injection of a long-acting toxic substance into the muscle belly.[33,34] About 0.5 to 0.8 cc. of 3% Rhaetocaine, an ethyl aminobenzoate preparation, produced a reversible degeneration in the muscle fibers that was maximal three to four days following injection, with gradual recovery ensuing. Also, the solution in the same

concentration will produce effective akinesia for 60 to 120 days.[35]

Testimony to the remarkable elasticity and reserve power of the extraocular muscles is the fact that in one badly invaded by secondary cancer and in another enormously stretched by a mucocele of the orbit normal functioning was not impaired.[36] As long as the nerves of these muscles are not compressed, they contract well. Yet, on the other hand, aging beyond 30 years is associated with progressive limits in the amplitude of ocular movements in all directions.[37]

A 30-degree head tilt was found to be accompanied by 5 degrees of torsion, a figure arrived at by measuring the change in the astigmatism axis.[38]

Last year I commented on the differences of opinion regarding torsion of the cornea and retina when the eye moved about an oblique axis in Listing's plane.[39] Apparently the subject was not closed. The latest facts are that "both corneal and retinal diameters extort when the eye turns upward, or downward and inward. . . . They intort in the other eventualities."[40]

Stimulation of the area that corresponds to the nucleus of Darkshevitch in the anterior periaqueductal gray matter of the midbrain causes a prompt inhibition of contraction of the extraocular muscles.[41]

Sensory Complications of Strabismus

Amblyopia.—Amblyopia exanopsia is described by Burian[42] as a selective cortical suppression of macular pattern vision which may be reversed. However, as he states, certain additional macular functions are abnormal—namely, the critical flicker fusion frequency is increased and the pupillomotor index is inverted. Light perception is normal; in fact, the amblyopic eye fixates better in dim light. In this respect it behaves like a normal dark-adapted eye.

The macular pattern vision is impaired in more than simply angular acuity, since the separation acuity is also affected. While an isolated letter can be distinguished, one in a row of letters of the same size is indistinguishable.[43-48] An instrument which spreads the letters to the desired separation,[45] projector slides with various separations between letters,[47] and a technique of pricking holes through black dots that are progressively smaller and more densely packed[48] have all been designed for training patients with this incapacity.

Burian[42] says that "loss of pattern vision . . . is reversible in appropriate cases." I would say that the word "appropriate" covers a multitude of disputed issues, judging from the voluminous literature bearing on techniques and results in the treatment of amblyopia that have appeared during the past year.

No one seems to be absolutely opposed to starting occlusion at a very young age. One author[49] did state that occlusion should only be done routinely up to 2 years of age and only be done exceptionally between ages 2 and 4. Many were very positive in their attitude that amblyopia treatment should be undertaken as soon as possible after onset of the strabismus, even in very young children or babies.[42,44,50-55]

There is no disagreement about employing occlusion in a preschool-age child as long as the amblyopic eye has foveal fixation ability. However, a number of authors disagree with the proposed merit of occluding if the amblyopic eye continues to fixate eccentric to the fovea after a one-week trial of patching.[45,56-67] In general, this same group advocates no patching for the school-age child, regardless of the type of fixation that prevails. Opposed to this point of view are those who demonstrate good results with simple protracted occlusion despite the amblyopic eye being eccentric at the outset.[51,52]

Probably the person who touched off this controversy was Bangerter.[68] As far as amblyopia influenced him, it appears that two major issues prompted him to develop new techniques: (1) the problem of diagnosing and treating the nonfoveal fixator and (2) the difficulty of improving vision by occlusion in the school-age child.

The matter of fixation eccentric to the fovea stimulated him to devise both a classi-

fication for it and a means of objectively diagnosing it. An ophthalmoscope with a small mark in the red-free green filter was used to project a nonilluminated spot on the retina. The patient was invited to fixate the spot, and with red-free light the examiner could observe whether the spot was fixated foveally, parafoveally, macularly, or paramacularly. A small star which projects at an angle of 1 degree and 10 minutes has been substituted for the mark on the filter, and this modification, incorporated into an ophthalmoscope, has been marketed under the name of Visuskop.* This technique of classifying fixation has been criticized,[58] owing to the difficulties of gaining subjective cooperation and the normal movements the eyes make while maintaining fixation.

For amblyopic children aged 4 and over having persistent nonfoveal fixation following one week of occlusion, and for all those of school age, regardless of the type of fixation, Bangerter[65] advocates a new discipline of therapy which he calls pleoptics. His greatest contributions are calling attention to the importance of (1) depressing the acuity of the pseudomacula while stimulating the true macula and (2) the possibility of enhancing the pseudomacula with occlusion. The pseudomacula is depressed by directing a beam of glaring light at it for several seconds, and immediately thereafter the true macula is stimulated with appropriate targets. Furthermore, he recognized the deficiency of separation of the amblyopic eye and outlined, as well as constructed, an instrument for treating this.[45] Coordination of visual stimulation with other senses (touch and hearing) and psychic functions (memory) also was applied by him.[68]

Refinements in therapy have been added to Bangerter's, and many ophthalmologists this year have described Cüppers major modification[59-66,69,70] in technique and instrumentation. Instead of depressing just the pseudomacula, as Bangerter did, Cüppers dazzled the entire posterior pole of the retina except the macula with strong light. An adaptation of the ophthalmoscope was developed which incorporated a small opaque disc in the center of the condensing lens. Thus, a nonilluminated area of either 3 or 5 degrees in the center of a 30-degree cone of intense light can be so directed as to shield the macula. The instrument is available under the name of Euthyskop.† A ring scotoma follows 30 seconds of exposure, and the protected macula is for the next few minutes in a relative state of hypersensitivity in comparison with the surrounding retina. The negative after-image is seen as a dark ring with a light central spot corresponding to the macula. The positive after-image is the inverse, except that in amblyopic eyes there is some difficulty in seeing the dark central spot. This can be facilitated by switching the light in the room off and on rapidly. As attention is called to the dark central spot, it will be noted to be surrounded by a luminous corona, but as seconds pass the black central positive after-image will gradually be erased, as evidenced by the color changes to violet, blue, green, and, eventually, white. In the meantime, the luminous periphery changes to a somber gray. At this point a macular target ("E" or letter symbol) is required to be fixated at 5 meters, its size being determined by the level of macular vision. At each session this cycle is repeated two or three times, e. g., illumination, after-image, inversion, and reading symbols. When vision has been improved by this method to 0.4 or 0.6, then foveal vision is considered to be present and occlusion is instituted. It has been expressed that maintaining the shield of nonillumination centered on the fovea is difficult,[63] even though the treated eye is completely atropinized. If a large esotropia causes the nose to hamper directing the light properly, the patient can hold a 60Δ prism before the fixating good eye.[62]

Results of Bangerter's pleoptics and Cüpper's after-image treatment vary according to the report one reads. Advocates of both

* Manufactured by Oculus.

† Manufactured by Oculus.

methods have claimed that visual improvement is hastened as compared with use of occlusion solely.[58-65] However, it has been demonstrated that occlusion plus conventional amblyopia training procedures (tracing, stringing beads, viewing detailed slides on major amblyoscope, etc.) provides a more rapid improvement than occlusion accomplishes unassisted.[71] Therefore, a quicker improvement in vision can be expected over what occlusion alone achieves by combining it with conventional exercises or by using either pleoptics or the after-image treatment.

No new statistics appeared this past year attesting to the quality of results attained by pleoptics. Concerning the permanence of improvement gained by pleoptics, a follow-up report of 208 cases which had been successfully treated was restudied.[58] Follow-up after an average of three and one-half years had elapsed since treatment showed 53% to be unchanged; 20% had improved further, and 27% had deteriorated.

The following series of cases points to the quality of results obtained by treatment with the after-image method of Cüppers: (1) 52 of 82 cases had vision improved to 1.0[59]; (2) vision of 0.9 to 1.0 was attained in 200 cases[61]; (3) vision in 23 of 70 cases was improved to 0.5 or better, but only 8 cases attained 1.0[64]; (4) 3 of 19 cases ultimately gained 1.0 vision[65]; (5) vision in 11 cases was improved to 0.4 to 0.6[60]; (6) 4 cases were unimproved that had been proven failures with previously tried occlusion therapy[69]; (7) bilateral amblyopes were unimproved.[72]

There are three papers which offset the claims made by the adherents of pleoptics and after-image treatment: (1) Comparison of two series of 100 children between age 5 and 12, treated with (*a*) occlusion and (*b*) occlusion plus conventional amblyopia exercises, reveals that each group ultimately obtained the same final result—only it was attained faster by combining exercises with occlusion[71]; (2) 60 patients treated with occlusion and exercises were claimed to have achieved results as good as pleoptics can provide[52]; (3) almost uniform improvement occurred in the eccentric fixation of 35 young children treated solely with constant occlusion.[51]

Treatment of amblyopia by the after-image method is very time-consuming.[69] From 30 to 90 sessions (30 minutes) are carried out daily, or at least several times per week.

Perhaps one reason pleoptics and after-image treatment of nonfoveal vision does not meet with even greater success is that neither offers significantly more active encouragement for foveal fixation than the passive method of occlusion. Granted that these methods, over previous methods of occlusion and conventional exercises, do more actively suppress the pseudomacula and encourage macular or paramacular fixation, still foveal fixation is hoped for rather than assured. The ultimate in treatment has not yet arrived which will invariably awaken the visual cortex to perceive the pattern projected onto the fovea of the amblyopic eye. In the meantime, the wisdom of (1) initiating occlusion as early as possible and (2) undertaking to educate the general practitioners, pediatricians, and parents about the importance of detecting visual impairment at a very young age impresses me as currently the most sound economical and medical policy to pursue.

Jaffe and Brock (1953)[73] observed that the after-image transfer phenomenon was abnormal in some amblyopic eyes and suggested this might be used as an indication of whether vision could be improved by treatment. With certain reservations, it is a subjective test to determine if foveal fixation is present, in contrast to Bangerter's objective Visuskop method. The nonamblyopic eye is exposed to the illuminated vertical bar of the after-image test while fixating the center target. Normally the patient can transfer the after-image from the nonamblyopic eye to amblyopic eye when the occluder is switched from amblyopic to nonamblyopic eye. Sometimes the ambly-

opic eye will appreciate no after-image transfer, and this result means nothing.[44] If the image-transfer is successful, one of three possible responses will be demonstrated by the amblyopic eye. The bar will (1) pass through a point fixated by the amblyopic eye, (2) intermittently waver in and out of the fixated spot, (3) constantly be displaced from the fixation point. The prognosis is good for visual improvement by occlusion if the after-image passes through the fixation point, questionable if it wavers, and poor if it is constantly displaced. Abnormal retinal correspondence makes all findings meaningless. Its value as a prognostic tool for treatment of amblyopia is attested to.[74]

Another idea for prognosticating whether vision can be improved is to use telescopic lenses.[44] If the vision is two lines better with them, it is capable of being improved by amblyopic therapy.

Concerning treatment, one new technique and one new concept were introduced this past year. It was advised that isoflurophate be instilled in the amblyopic eye, if hypermetropic, and that the nonamblyopic eye simultaneously be atropinized.[75] A new concept was presented to the effect that visual acuity measured in Snellen standards is not what we should abide by in evaluating relative visual ability of the two eyes. Rather, fixation preference is the more logical standard, and amblyopia therapy should be carried on until fixation preference is switched.[43]

Suppression.—Statistics on suppression among 562 strabismic children below 13 years of age appeared this past year.[76] Suppression was present among 49% of the entire group, 52% of esotropes and 23% of exotropes. The younger the age of onset the higher the incidence of suppression—63% in those whose heterotropia developed before 18 months, 48% in those between 18 months and 4 years, and 36% if the strabismus started after age 4. In temporary squint suppression occurred in only 7%, whereas in constant squint it was present in 62%. If the squint was alternating, the suppression occurred in 67%, and if it was alternating hyperphoria the incidence increased to 85%.

No new concepts of pathophysiology of suppression were encountered, but many little useful tips in examination and treatment came from one author.[77,78] An example is emphasizing the observation of the patient's eyes while awaiting the reply to the query of whether "one" or "two" is seen. If the eyes move, the examination is invalid. If the patient sees "one" with no movement, the cover test offers a quick way to determine if the reply indicated fusion or suppression. No movement by cover test is evidence that no suppression exists. Another tip is to not use a light for fixation while routinely investigating for suppression, since it is artificial and an integral part of the technique for breaking down suppression. Consequently, partial suppression to commonplace viewing may ordinarily prevail, but not during fixation of the light. Any small object, such as a button, may be used for fixation. In the event diplopia cannot be aroused, the examiner proceeds to using the light, a red filter, and even displacement of one image by introduction of a prism before one eye. In breaking down suppression the red filter is heavily relied upon, with the goal being to develop control of fixation, first for the red and then for the white object. If motor fusion is present, the attempt is then made to fuse the two into a "pink." If a white card is used as a fixation target, the card will be "pink." If words are on the card, while it is read the consciousness of a "'pink" background is retained. An effort is made to keep the words free of diplopia, which is a necessary step in converting from peripheral fusion (pink background) to foveal fusion (no diplopia in words). Physiological diplopia and bar reading are the final accomplishments to be mastered after peripheral and foveal fusion are secured with the red filter.

Abnormal Retinal Correspondence.—Unanimity of opinion is still lacking as to whether abnormal retinal correspondence (ARC) is the cause or effect of squint. A new slant on the old concept that ARC is a sensorial adaptation to misaligned eyes was expressed in the hypothesis that the deviating eye in some squints may become active and begin to assert itself right along with the fixating eye on matters of localization.[79] Prior to demonstrating such independence, the deviating eye had suppressed its own inherent localization system (NRC) accepting subordinance to that localization performed by the fixating eye. But finally the deviating eye broke away from such subsurvience and began to enjoy the liberty of localizing according to a new system that compensated for the degree of misalignment. On the other hand, dissatisfaction has appeared from two sources concerning ARC as an effect of heterotropia. One author questioned how ARC could result from misalignment when it occurred in intermittent strabismus and when the angle of ARC was different from that of the squint.[80] A second author based his dissention on the fact that in seven cases of congenital incomitant squint the binocular vision was normal and ARC was lacking.[81] He reasoned from these seven incomitant cases that congenital concomitant squint cannot cause ARC and that when ARC is found in a congenital concomitant squint it is the cause of the squint and not the effect.

The depth to which ARC develops is entirely individual. It is probably so tenuous in some that the coarseness of our clinical investigation is insensitive to its presence. And it may be so evanescent as to be present one moment and then replaced by NRC for the next moment.[54,82] Such factors as size and nature of angle, age of onset, duration, and constancy of strabismus have been related to the presence of ARC as well as to the depth to which it has developed. But even on these matters there is disagreement. The size of the horizontal angle of squint has little influence[54] according to one author, but the contrast to this is found in the statement by another "that abnormal correspondence appears chiefly in small angles of squint."[76] These statements are reminescent of Travers' (1936)[83] claiming that ARC in squint angles of less than 10 degrees is "very unlikely" and Jampolsky's (1951)[84] reporting that 90% of cases with less than 15△ of strabismus have unharmonious ARC. Apparently ARC incidence is not increased if the horizontal strabismus has associated with it a vertical anomaly. In 154 patients with a horizontal squint only and 136 having a vertical factor in addition to the horizontal one, there was ARC of 27% and 25%, respectively.[85]

The age of onset was found to have a great bearing on incidence of ARC; it was 95% in those with congenital strabismus, 77% if the squint started between 6 months and 2 years, 56% if between 2 and 4 years, and 6% if it first developed after 4 years.[54] Yet, another author contradicts this by stating that ARC is not related to an early appearance of squint.[76] Duration of squint is considered of some significance; 30% had ARC if the squint had been present from 6 months to 6 years; 70%, if the duration had been from 5 to 10 years; 58%, for 10 to 20 years' duration, and 90% if it had been present for more than 20 years.[54] There is no disagreement that the greatest single factor required to produce ARC is constancy of deviation.[54,76]

Even if ARC is accepted as being the result of a positive attempt by a squinter to enjoy binocular vision, certain attributes of binocular vision as experienced by nonsquinters are not entirely appreciated. Stereopsis and motor fusional amplitudes are usually lacking even though sensory fusion is present at the subjective angle.[82] I recall that Levinge (1954)[80] found that 50% of ARC cases were accompanied with stereopsis and 62% had physiological diplopia.

"Side-jerk" is the phrase used to describe the conjugated movement with prompt redress that occurs during the prism and alternate cover test in certain alternating

esotropes of long standing, even though the angle of strabismus has been fully compensated with prisms. It is suggested that such a pattern is indicative of the depth to which ARC has advanced.[87]

Nothing revolutionary in instrumentation or technique has appeared for diagnosing the state of retinal correspondence. A modification of the synoptophore or amblyoscope has been devised in the form of a homemade haploscope which is used at 5 ft. rather than 13 in., with superior results having been claimed.[88] The after-image test has been adapted to the Heiland Strobonar I electronic flash unit, which produces an intense stimulus for only 1/1000 of a second. This is used after dark adaptation has been induced with the red plastic goggles worn by radiologists.[89]

A logical classification for categorizing sensorial relationships as determined by a major amblyscope has been presented. It breaks NRC into (1) fusion at the objective angle and (2) "jump" suppression at the objective angle. ARC has been divided into (1) fusion at the subjective angle, (2) "jump" suppression at the subjective angle, (3) fusion between objective and subjective angles, and (4) "jump" suppression between objective and subjective angle.[90] In England and Australia the last group (fourth type of ARC) would be referred to as having lack of NRC.[7] The importance of pointing out this distinction is that here probably lies the crux of the confusion that perpetuates and even magnifies itself each successive year in the literature that bears on the incidence of ARC and the indications for and results of treatment of it. It it well recognized that the fourth group ("jump" suppression between objective and subjective angle) is the best suited for therapy when one is considering prognosis. Therefore, when the British literature quotes statistics as to prevalence of ARC and speaks of poor therapeutic results,[7,91,93] one should keep in mind that this ARC group which we, in this country, consider most favorable for treatment has not been included in their ARC classification. And this is no small matter, since among 81 patients diagnosed as having ARC by the author who presented the above classification 38 were of the type with "jump" suppression between objective and subjective angle.[90]

The after-image test is integrated with the major amblyoscope findings in order to formulate a prognosis for treatment.[93] If the depth of ARC is only to the degree that there is a normal after-image response in the presence of a synoptophore finding of suppression at the subjective angle, treatment may justifiably be tried. If no improvement follows in six sessions, it should be discontinued. With success, the sessions can be extended to 20 or 30. Yet, another author feels that it is unfair to discontinue treatment after 6 to 12 sessions when no improvement has been attained since so many times progress is slow and with perseverance it may be forthcoming.[82] Still another author reports[94] 85 ARC cases, confirmed by after-image test, of which 15 were normalized by preoperative patching and bifoveal stimulation, 13 were converted to NRC by postoperative orthoptics, and 2 more were cured by some unlisted means. Therefore 30 out of 85 patients with ARC with after-image findings compatible with such a diagnosis were cured. Now, were these ARC or were they absence-of-NRC cases?

Early institution of alternate occlusion[67] and early surgical correction of the misalignment[82] to prevent ARC developing or deepening are not new ideas. One report tells how ARC in 7 of 9 cases of 3-year-old children and in 10 of 11 cases of 4-year-old children was converted to NRC with occlusion and surgery.[90] The same treatment for children aged 5 and older with ARC yielded no more than 50% success. In Britain very few cases of ARC are encountered in areas where surgery has been done early, but in other districts, where the angle of squint has been treated only with glasses, or nothing, until school age, the incidence is appreciably higher.[92] Australian statistics show that 70% of patients have NRC following

surgery done before 3 years of age and only 27%, if the surgery is delayed until after 10 years of age.[54]

Criterion for cure of ARC must include stereopsis accompanying the newly acquired NRC.[88] No reference was made as to the quality of stereopsis.

Emphasis is placed on the importance of peripheral fusion in maintaining a good result obtained from surgically correcting a squint associated with monolateral amblyopia.[95] Peripheral fusion and NRC are thought to be separate expressions of the same entity, since among 15 unilateral amblyopia patients whose eyes remained straight after surgery, all but 2 demonstrated peripheral fusion and NRC. ARC to the after-image test was present in one of the two having no peripheral fusion. On the other hand, in 10 similar cases the eyes drifted away from their ideal immediate postoperative position and in none was peripheral fusion elicited, but 7 had ARC.

Heterophorias

Convergence insufficiency has been found in 8%,[96] 10%,[97] and 25%[98] of patients seen in private practice. Statistics as to its frequency undoubtedly vary according to the care the examiner exerts on suppressing the fusion reflex and controlling the accommodative convergence.[99] The 20-40 years of age group had the highest percentage of convergence insufficiency.[98] This syndrome of greater "exo" at near, poor prism convergence amplitude, and remote near point of convergence (NPC) was attributed to some vague breakdown in convergence.[100] Undercorrected myopia and overcorrected hypermetropia[96,97,101] were occasionally associated, but more often convergence insufficiency developed secondarily in untreated primary divergence excess.[97] Not only should treatment include the usual convergence exercises, but also physiological diplopia should be taught, so that lack of proper convergence response to the convergence stimulus will result in diplopia and not in suppression.[102] As a rule, this condition is most satisfactorily treated by orthoptics.[103] The objective sign of recovery is measured by increase of convergence amplitude, and the usual goal seems to be at least a recovery point of 40Δ.[96] Subjectively the sign of recovery is lack of eyestrain symptoms while doing close work.[100] Other than orthoptics, there remains the prescription of base-in prisms.[104]

Vertical phorias are primarily treated with prisms. The enigma is what percentage of the measured hyperphoria should be corrected. One prominent authority usually corrects for three-quarters of the deviation.[105] This is criticized by another, who advises the ophthalmologist to judge on an individual basis how much of the fusional amplitude can be comfortably used to compensate for the phoria.[104] Yet, the fusional amplitude in itself is anything but absolute. For example, there can usually be elicited an immediate normal vertical amplitude of about 3Δ. However, with small slow increments of vertical prism beyond this immediate finding, the amplitude can usually be extended to 6Δ. Moreover, the 6Δ vertical fusional amplitude was maintained in five of 7 subjects for an indefinite period with comfort. Therefore, the author advises recourse to trial of prisms in clip-overs to determine whether the symptoms are improved.[106]

Pupillary hypophoria or hyperphoria is introduced as a new term.[107] In any type of optically corrected ametropia, regardless of the displacement of the pupil in corectopia, the image cone is brought to focus on the fovea. If the uncorrected high hypermetropia of aphakia is associated with a superior or inferior corectopia, the truncated cone will project its image circle above or below the fovea, respectively. On alternate cover there will be a movement downward of the superior corectopic eye, and upward if the corectopia is inferior, in an effort to move the image circle onto the foveal area. This could be misleading to the examiner, who might confuse it with primary vertical muscle imbalance. How-

ever, the vertical image disparity will vanish at the time an aphakic correction converts the truncated image cone into a sharply focused one.

Accommodative Esotropia

Some 90 years after Donders (1864)[108] related hypermetropia to esotropia, a different concept as to the importance of this relationship has come out of the Netherlands. Since the majority of hypermetropes do not squint and a large percentage of squints have small to moderate hypermetropia, accommodation as the primary cause of squint in hypermetropia is criticized.[76] A unitarian concept of etiology—that all strabismus is the result of deficient maturation of sensory and/or motor fusion reflexes—reduces hypermetropia to a secondary factor which may trigger off the conversion of latent tropia to one which is manifest.

Study of hypermetropia and esotropia among identical twins has resulted in deductions diametrically opposed to the unitarian concept.[109] In six of seven sets only one twin had strabismus; yet all but one set had identical ametropia. Since identical ametropia in each twin was associated with strabismus in but one twin, it was concluded that no genetic lesion accounts for deficient fusion reflexes. Were there such a defective gene, each identical twin should have developed a squint. Instead, the ametropia was considered the prime etiological factor, while the interplay between accommodative convergence and normal fusion reflexes determined whether squint developed.

Explanation of the problem of greater or lesser esotropia at near fixation than at distance continues to be a challenge. Acceptance of the thesis that the convergence center is balanced by a divergence center is becoming more popular, particularly since Adler (1953)[110] demonstrated a burst of electrical activity in the lateral rectus immediately preceding a divergence movement and Breinin and Moldaver (1955)[111] electromyographically showed the firing of motor units to be increased in the lateral rectus when the eye broke from fusion into exotropia. Convergence is considered a near function, while divergence is a distance function.[97,112] Esotropia that is greater at near is attributed to a hyperactive convergence center abnormality, whereas esotropia greater at distance indicates a hypoactive divergence center.

Without attempting to explain the pathologic physiology of greater esotropia at near than at distance, practically all contributors recognize this to be a facet of accommodative esotropia not related to hypermetropia.[75, 113-119] Therefore, something more than correction with ametropic spectacles is needed to treat it. Bifocals are easily the most widely accepted therapy for this nuisance, assuming that binocular vision is possible at distance with glasses. Isoflurophate (DFP) also is used in conjunction with single-vision lenses rather than bifocals.[75,117]

Tonic convergence[24,115] is the basic tonus of the convergence apparatus, distinct and apart from accommodative and fusional convergence, which in conjunction with tonic divergence determines the basic alignment of eyes. The basic alignment is measured by prism and alternate cover at distance with glasses while small symbols are fixated. In proportion to the quantity of basic "eso,"[114, 116] determined according to the above method, tonic convergence is a factor aggravating accommodative esotropia. If this is significant, surgery may be indicated, but caution should be exercised not to correct any more "eso" than that which is basic.[114-117]

Tonic divergence opposes tonic convergence[115,117] and in conjunction with fusional divergence compensates for the accommodative esotropia.

I am of the opinion that basic alignment is not altered by orthoptics, but one author speaks of modifying the "distribution of tonic reciprocal innervation" by exercise.[115] Dissociation exercises work their benefit through increasing the fusion divergence amplitude.[113,114,116,120] To check accurately whether the amplitude has been increased, it should always be measured relative to a

fixed amount of accommodation (relative fusional divergence).[113,114,116]

Isoflurophate is a valuable diagnostic tool for eliciting the accommodative factor in esotropia.[75,121] Beyond this limited use there is disagreement as to its justification. It is claimed to be as good or better than glasses if the hypermetropia is below 4.50 and not complicated by astigmatism. Use of isoflurophate, rather than bifocals, for the excessive near convergence has already been mentioned.[75] The prolonged instillation, difficulty of maintaining a constant concentration, extreme miosis, frequency of iris nodules, and drug cost constitute a magnitude of disadvantages that outweigh the advantage of not wearing glasses.[121] Substitution of isoflurophate for glasses during swimming or in summer camp is a worthwhile endeavor.[75] Allergy to the medication developed in 3 of 277 cases.[75]

It was first recorded by Vogt (1920)[122] that nodular excrescences developed along the pupillary border with pilocarpine and with physostigmine therapy. Since interest in isoflurophate treatment of esotropia has broadened, attention to the frequently coincident pigmented nodules has increased. It has been natural to refer to these nodules as cysts, since most hypotheses about their formation include entraping of fluid either between separated layers of the iris epithelium or within iris clefts which have been purse-strung by sustained iris sphincter contraction.[123] The first microscopic study of isoflurophate iris nodules is illuminating in many aspects.[124] The specimen was an aniridic eye, with only a rudimentary iris; still, iris nodules indistinguishable from those that appear in normal irides developed with isoflurophate therapy. There was a new growth of iris pigment epithelium, which overlapped the pupillary border as a solid finger-like nodule. In some areas the epithelial layers were split, forming cystoid fluid-filled spaces permeated with pigment. The root of the iris and ciliary processes was also involved in the hyperplasia of pigment epithelium. Certainly, iris sphincter spasm did not induce this clinical picture in an aniridic eye.

The use of pilocarpine is advised[125] because of the ill effects of intraepithelial cysts resulting from isoflurophate. However, the "cysts" apparently are due to parasympathetic stimulation of the pigment epithelium[124] and have been observed in eyes treated with pilocarpine, a diethyl *p*-nitrophenyl phosphate (Mintacol), physostigmine (Eserine), and neostigmine (Prostigmin).[126]

Nonaccommodative Esotropia

In this country the etiology of strabismus is widely accepted as being diverse.‡ Anatomical, refractional fusional defects and hyperconvergence reflex each enjoy the distinction of being judged an integral entity comprising the list of factors that cause ocular misalignment. Previous comment has been made on the theory currently popular in the Low Countries of Europe which ascribes all strabismus to one cause. A maturation defect in the sensory and motor fusion reflexes is suggested as being due to a disturbance of myelinization in the occipital lobe.[50,76,127] Supporting this concept is the often-encountered final result of no fusion, regardless of the treatment pursued in congenital esotropia. If fusion is considered to be instinctive, then when no fusion occurs despite refraction and misalignment factors being relieved, at the earliest possible age, the inference is that a congenital central defect precludes fusion.[128] Also, brain damage is known to be associated with a high percentage of strabismus, and now prematurity has been implicated in a similar way; 2.3% of prematures developed esotropia as compared with 1.4% of full-birthweight babies.[129] Congenital esotropia and its higher incidence among children with cerebral hypofunction and prematures underscore the importance of an abnormal fusion mechanism, but it is difficult to accept this as the core of every squint problem.

Because of the excellent results from early surgery for permanent esotropias that com-

‡ Adler, in discussion on Keiner.[127]

menced at age six months or later, a Swedish ophthalmologist [130] reasons that at least 70% are mechanical. Altering the position of the eye in the muscle ring early after squint onset (0.5 to 4 years) provided lasting functional cures (9 to 17 years) in at least 55% of the children without any assistance from orthoptic treatment.

Late onset of comitant esotropia is an unexplained problem. It was transient in an 18-year-old girl [131]; two cases developed in a much older age group—58 and 63 years,[132] and four siblings became esotropic, three at 6 years and one at 9 years.[133]

Published reports still appear which accuse orthoptics of being valueless in the treatment of strabismus.[134] Statistics extolling its merits are criticized on the basis that careful selection of cases for treatment influence the result, with the consequence of slanted and varied deductions being formulated about its value.[53] But in most areas ophthalmologists are maturing in knowledge of orthoptics and more keenly appreciate its potential, as well as limitations. Orthoptics will not overcome misalignment, it being solely an adjuvant to surgery, optical, or medical treatment in establishing binocular vision in some patients of sufficient age.[94, 135-137] Orthoptics is not only useless but dangerous in the event that surgery has not put the globes in the correct position.[136] The claim is made that functional cures are twice as frequent if orthoptics is used in conjunction with surgery as compared with surgery alone.[94] On the other hand, if fusion can not be encouraged before surgery, orthoptics is usually unable to develop it after surgery.[137] Prior to operation fusion is most desirable, even if ARC is the response to simultaneous macular perception targets. Despite the correspondence being normal, orthoptics is abandoned if the findings indicate an inability to fuse.[54]

Among various objections listed against early surgical correction of nonaccommodative esotropia is the lack of opportunity to follow through with immediate postoperative orthoptics.[56,59,138-140] The issue is also raised that a complete diagnostic work-up is impossible in a very young patient.§ Furthermore, the same author calls attention to the fact that small-angle esotropias are more difficult to treat orthoptically than large-angle squints and that frequently early surgery merely converts large angles to small ones. Still additional caution about early surgery is advanced on the grounds that there is a tendency for esoposition to lessen during childhood, which is probably explained by a reduction in tonic convergence.[141] An observation is made that the percentage of functional cures is approximately the same for the two groups operated upon between 0-3 years and 4-5 years.

Definitely, there is a minority group which advocates only preventive treatment of amblyopia and ARC (occlusion and glasses) until attainment of a minimum age of 4 but more usually 5 to 6,[59,140] or perhaps even 7 years,[138,139] before integrating surgery and orthoptics. By far the majority, however, have more faith in Mother Nature and consequently advise eradication of sensory (amblyopia) and motor (misalignment) obstacles at a very tender age. The literature is heavy with statistics and "off the cuff" opinions vouching for the merits of early surgical correction, but there is a still wide latitude among writers as to what constitutes early when measured in chronological age. Some claim they have no rigid minimum age by which they abide, meaning I suppose, that the surgery is done as soon as the size of the angle is known and the vision of each eye equal, even if it be age one year or less.[92,94,128,130,141-147] Or surgery between age 1 and 2 is considered by another to be very early [54]; age "2 or so" is referred to [53]; 3 to 4 [148] and even 3 to 5 [149] is thought by others to be early surgery. The greater percentage of congenital esotropes operated on early do not spontaneously develop perfect binocular vision; however, peripheral fusion is permitted to develop, and this is important, since it enables the little child to exercise better visual

§ Cüppers, in discussion on Thomas.[46]

judgment.[128] The psychological and emotional benefits from straight eyes during early formative years are not to be lost sight of either.[142,144] But the benefit of surgery prior to 1½ to 2 years of age in congenital esotropes is questioned on the assumption that some retardation of development is most likely present in the nerve structures subserbing sensory and motor fusion.[141] Granted that such an assumption is valid, who can say at what month of chronological age the retarded development will have caught up to normal, or will ever catch up?

Two novel techniques in surgery on ocular muscles appeared this past year. One is the "electric knife," which is used for incising the conjunctiva, separating Tenon's capsule, and cutting the muscle from its insertion.[150] The other consists of injecting hyaluronidase into the muscle and passing a nylon suture through it, then forcefully stretching this muscle by pulling and securing the globe far out of its field of action. The suture is left in place with tension on the muscle being adjusted as need be for two days to three weeks.[151]

One of the complications of surgery for esotropia is postoperative divergence, which is claimed to be more frequent if the medial recti are recessed than if the lateral recti are resected.[152] Adhesions between the recessed muscle and the sclera have been cited as one possible cause for adduction weakness.[153] The opposite effect, of abduction inability, has been recorded as due to abnormalities between the conjunctival tissues and tenotomized or recessed medial rectus.[154] Medial rectus palsy is simulated in some recession resection cases owing to firm resistence of the surgically shortened lateral rectus, which demonstrates a positive forced duction test when adduction is attempted with use of anesthesia.[155] Recessing the previously resected lateral rectus corrects this complication.

Stereopsis on the synoptophore is apparently no more reliable than proof of bifoveal fixation, as determined by the cover test, or demonstration of at least a 10-degree fusional amplitude that the patient habitually relies on binocular seeing habits for commonplace seeing.[156] Research was conducted to determine the correlation between stereopsis on the synoptophore and binocular depth-perception ability. Among treated strabismus patients achieving stereopsis on the synoptophore, only 1 out of 10 of the postoperative group and 2 out of 10 of the group treated solely with orthoptics and requiring no surgery had binocular depth perception that was normal. Unfortunately, it appears that the stereopsis investigations were ungraded and this finding was compared with keenly graded binocular depth-perception tests. Had more emphasis been placed on comparably grading each test, perhaps there would have been some accord in the binocular parallax involved in each test. But, overlooking this criticism, the study indicates that the best binocular depth perception occurred among postoperative patients with gross stereopsis who had a short interval between onset and operation. According to the authors, "these results suggest that operation should not be postponed until the presence of fusion can be ascertained." They conclude that patients with stereopsis on the synoptophore, but without good quality binocular depth perception, depend mostly on uniocular clues for depth appreciation and peripheral fusion for maintaining parallel visual axes.

Fixation Disparity

This years' literature treats fixation disparity as a phoria, since extramacular fusion is present despite the coexistence of such tropia features as manifest absence of intersection of the visual axes at the object of regard and presence of amblyopia and central suppression.[157-159] Moreover, the reader may obtain the impression that fixation disparity occurs only secondary to a prior existing tropia, since there was no mention of the syndrome ever being primary and unassociated with antecedent accommodative or nonaccommodative esotropia. However, this oversight is due to, I presume, emphasis

having been placed on comparing small-angle esotropias with fixation disparity.[157, 159]

Differentiation of fixation disparity from small-angle esotropias is not easy. Smaller measurements by cover-uncover test than those of alternate cover are suggestive that a fusional motor response reduces the angle to within Panum's fusional space and fixation disparity is probably the correct diagnosis.[157] Demonstration of ARC, however, is indicative that the small angle disclosed by cover test is esotropia and not fixation disparity.[157] The small "eso" deviation that cannot be classified according to the above two criteria is the one that defies diagnosis. It is suggested that if a large angle is reduced to a small one by (1) glasses or (2) surgery we should suspect fixation disparity in the former case and small-angle esotropia in the latter.[157]

It should also be borne in mind that demonstration of ARC in small-degree esotropias is fraught with difficulty and uncertainty, so much so that the whole problem of differential diagnosis resolves principally into a matter of academic interest. Particularly is this the case when it becomes apparent that neither small-angle tropia nor fixation disparity are easily amenable to cure by orthoptic, surgical, optical, or medical means. And seldom are symptoms (cosmetic or asthenopic) sufficient to make therapy necessary. In the past, most of the treatment of these small esodeviations has been the result of the ophthalmologist's prodding the patient rather than the other way around.

In the young, fixation disparity may spontaneously disappear, in fact, we are told that often it is a self-limiting entity.[157]

Divergent Strabismus

Divergent strabismus developed in 2.3% of prematures as compared with 0.9% incidence among full-term children.[129]

Attention is directed to the one of the frequently encountered sensory patterns associated with exotropia for distance but fusion at near.[7] The diplopia test, afterimage test, and major amblyoscope test for distance all indicate homonymous diplopia. The right eye sees the right image and the left eye sees the left image, no matter what horizontal prism is introduced or how the arms on the amblyoscope are arranged. This peculiar panoramic anomaly suggests "a reversion to an atavistic type of innervation of the eyes."

The divergent patient that is without a subjective angle on the synoptophore, meaning an absence of NRC when diverging, often fails to appreciate diplopia or learn NRC by preoperative orthoptics; yet the surgical results seem to not be any the worse in this type of case.[160] Diplopia is usually readily appreciated after surgery if the condition has been slightly overcorrected.

Orthoptic treatment and surgery seem to be interwoven into the same principal disagreements as to how best therapeutically to approach divergent strabismus. In general, there is no dispute that surgery is the crux of the treatment. The zone of indecision starts when one inquires into the following problems: (1) what age surgery should be done, (2) whether orthoptics should be employed, and whether (3) orthoptic treatment should be preoperative as well as postoperative.

Separation of opinions on this matter of the best age for surgery appears primarily due to differences regarding the necessity of using orthoptics along with surgery. Two surgeons advise early surgery, below the orthoptic age, in order to prevent secondary convergence insufficiency becoming superimposed upon divergence excess as well as to avoid the possible appearance of sensory complications.[161,162] Orthoptics is advised, by another author, to be held in readiness in the event the desired result does not automatically postoperatively appear, but the surgery is advised to be deferred until 5 to 6 so that orthoptics may be used if necessary.[163] Combining orthoptics and surgery is advised by the majority,[92,94,160,

[164-166] which means this group recommends surgery after the age of 4. The ease with which the younger group (age 5) tolerates surgery from a psychological point of view and the difficulties encountered on this score in the older children are emphasized.[166]

Usually four preoperative orthoptic sessions [166] and four to six postoperative ones [160,166] are sufficient to produce an ideal result in England. A much greater volume of orthoptics is used, however, in Sydney, apparently because the surgeons have a philosophy about the treatment of intermittent exotropia which allows them to operate only upon the orthoptic failures if the squint is over 15 degrees.[167]

The danger of esotropia following recessions of the lateral recti in cases that have large divergent deviations for distance and small deviations for near has caused one operator to try recessing one medial rectus along with the lateral recti recessions.[168]

Horizontal Noncomitant Strabismus

In lateral rectus paralysis the horizontal deviation is maximal on looking down, while in medial rectus palsy it is greatest on upward gaze.[169] Consequently, there is a compensatory face turn toward the ipsilateral shoulder of the paralysed lateral rectus, with chin depression. In association with medial rectus paralysis the face is turned away from the involved eye and the chin is elevated.[170]

Combining lateral rectus resection with the Hummelschiem operation provides an abduction of approximately 40 degrees in lateral rectus paralysis.[171] A procedure similar to that of Hummelschiem was performed for absence of the medial rectus.[172] The nasal halves of the superior and inferior recti were transplanted to the former insertion of the medial rectus, the remaining temporal halves were moved nasally 4 mm., and the lateral rectus was recessed. The result was 23 degrees of adduction ability.

Bilateral paralysis of adduction and abduction with 30△ of total horizontal fusional amplitude is described in which the forced duction tests under anesthesia were positive.[173] Surgical exploration revealed the involved muscles to be inserted posterior to the equator.

From the Mayo Clinic came a report on acquired paralysis of ocular muscles that occurred over a 10-year period.[174] Regardless of the particular cranial nerve involved, the four commonest diagnosed causes were head trauma, neoplasm, vascular changes, and aneurysm. Paralysis of the third nerve resulting from head trauma is explained in some cases by cerebral rotation or displacement upon impact of the anterior temporal part of the skull.[175] Poliomyelitis was listed as causing two incidents of sixth nerve paralysis,[174] as well as several other paralytic strabismus cases.[176] Diabetes is associated in a high percentage of the acquired paralytic squints having a vascular etiology.[174,177-179]

Vertical Strabismus

Ocular torticollis neutralizes the visual symptoms of a cyclovertical muscle imbalance which, in turn, induces a compensatory scoliosis [180] which persists regardless of whether fusion is retained.

The selection of the proper surgical approach to correct paralytic strabismus is facilitated by dividing the 12 extraocular muscles into three groups of 4 muscles each [181]: (1) horizontal recti, (2) right vertical recti and left obliques, (3) left vertical recti and right obliques. Confining surgery to muscles within the group that encompasses the paralysed muscle will not do violence to horizontal, vertical, and torsional factors that have to be weighed in any proposed surgical correction. For example, the chance of attaining a functional result will not be enhanced in cyclovertical muscle paralysis if the surgical procedure corrects the vertical error but aggravates the torsional component.[182] And such is the consequence if the surgeon does not confine his operations to within the group of which the paralyzed muscle is a member.

Surgical correction of overaction of the inferior obliques associated with esotropia

is generally advised against, since it is considered to be functional to the adducted position of the eye and will probably disappear when the esotropia is corrected.[54] Since no author was discovered this year to advocate the opposing point of view, I feel constrained to express my conviction that seldom does a well-established overaction of the inferior obliques spontaneously vanish after the horizontal tropia has been eliminated. Consequently, it is felt that there is merit in combining the surgical correction of both at the same operation.

Recession of the insertion of the inferior oblique is recommended, since its results are more predictable than mutilative myectomy, and myotomy consistently produces little, if any, effect. Furthermore, its sheath can be completely exposed and any anomalies that may be detected are directly dealt with.[183] Despite the trend toward wide acceptance of recessing the inferior oblique, an Italian report shows that one to three 2 to 3 mm. incisions into the lateral inferior border of the muscle, exposed through the cul-de-sac, are useful in cases of slight hyperfunction of the inferior oblique.[184] This procedure, in 33 cases, corrected 2 cases to 4△ in the primary position and 3 to 8△ in the vertical field of action of the myotomized muscle. Isolated procedures on the inferior obliques in 34 cases were not found to alter the horizontal position of the eyes significantly.[185]

A case of traumatic acquired bilateral superior oblique paralysis was well corrected by bilateral myotomy of the inferior obliques and bilateral tucking of the superior obliques—all done at one surgical intervention.[186]

The syndrome of inferior oblique paralysis with impossibility of forceful elevation of the adducted eye with forceps under anesthesia has been described again this year.[187] But a warning has appeared that the above findings do not automatically diagnose the superior oblique tendon sheath syndrome.[188] Such findings may be encountered also with anomalous inferior oblique check ligaments and in an abnormality of the trochlea that creates a dystocia for free slippage of the tendon.

Esotropia with apparent overaction of the superior obliques on lateral versions was studied in 124 cases.[189] The esotropia is increased in elevation and diminished in depression. This is graphically described as the "A" syndrome,‖ or the tent or tepee (A) syndrome.¶ The increase in esotropia on looking up is hypothecated to be due partly to insufficiency of the lateral rectus muscles. The attempt to keep the eyes straight at near, especially when looking down, provokes inhibition of the medial recti in co-contraction with the weak lateral recti, which accounts for less esotropia in this position.[189] This reasoning is completely the reverse of observations previously reported.[169,170] (see Horizontal Noncomitant Strabismus). No various combination of surgery on the horizontal acting muscles altered the "A" syndrome.[190]

Alternating hyperphoria really "found itself in for a going over" this year. The frequency was found to be 9% among 922 squinting Amsterdam children.[76] Its pathologic physiology, which heretofore has been extensively accepted as innervational, was redescribed by a Dutch ophthalmologist.[127] But a new concept was introduced to explain the upward deviation and excyclotorsion of the usually adducted dissociated eye.[191] It was reasoned that the primary problem was a torsional deviation caused by relatively stronger extorsion resulting from an abnormally high inferior oblique insertion which was not offset by superior oblique intorsion. As the dissociated eye extorted, the inferior oblique also became a more efficient adductor, and with increased adduction the elevating action of this muscle was enhanced. If the abnormality was bilateral the dissociated eye upon assumming foveal fixation would intort, depress, and abduct, while the dissociated eye, which just surrendered foveal fixation, would ex-

‖ Albert, D. G.: Personal communication to the author.

¶ Jampolsky, A. J.: Personal communication to the author.

tort, according to the Law of Hering, but also adduct and elevate, owing to the peculiar mechanics of the situation. At least, this concept is in agreement with Hering's law, which is denied by the innervational explanation.[127] Would not electromyography be feasible in adjudication of this disputed issue?

Surgery based on the mechanical conjectures stated above is claimed to produce satisfactory results.[191] The muscle insertions must be moved horizontally, vertically, and torsionally in various combinations to eliminate the primary torsional problem as well as the secondary contractures that have built up with time.[191]

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News and Comment

ANNOUNCEMENTS

Home Study Courses.—The 1957-1958 Home Study Courses in the basic sciences related to ophthalmology and otolaryngology, which are offered as a part of the educational program of the American Academy of Ophthalmology and Otolaryngology, will begin on Sept. 1 and continue for a period of 10 months. Detailed information and application forms can be secured from Dr. William L. Benedict, the executive secretary-treasurer of the Academy, 15 Second St. S. W., Rochester, Minn. Registrations should be completed before Aug. 15.

Orthoptic Training Available.—The Ohio State University, Department of Ophthalmology will begin the next orthoptic course in September, 1957. This is an intensive nine-month program, combining basic science and practical work. No fees are charged, but the student must support herself during the training period. Inquiries should be directed to Dr. William H. Havener, Department of Ophthalmology, Ohio State University, Columbus, Ohio.

South Carolina Society of Ophthalmology and Otolaryngology and North Carolina Eye, Ear, Nose, and Throat Society.—The joint annual meeting of the South Carolina Society of Ophthalmology and Otolaryngology and the North Carolina Eye, Ear, Nose, and Throat Society will be held in Hendersonville, N. C. The dates are Sept. 15-18, 1957. Headquarters will be the Skyland Hotel.

The following guest ophthalmologists will be on the program: Dr. E. A. Maumenee, Baltimore; Dr. P. G. Leinfelder, Iowa City, and Dr. Alston Callahan, Birmingham, Ala. Likewise, the following otolaryngologists will be on the program: Dr. Francis Le Jeune, New Orleans, and Dr. J. W. McLaurin, Baton Rouge, La. The third otolaryngologist will be announced shortly.

Hendersonville, N. C., is located in the Blue Ridge Mountains and is a particularly lovely spot at this season of the year. A large attendance is anticipated.

Postgraduate Ophthalmology Courses.—Five courses in ophthalmology for specialists are being offered by the New York University Post-Graduate Medical School during the first half of the 1957-1958 academic year. These courses are the following:

Histopathology, a part-time course, Sept. 16 through 20, given under the direction of Dr. A. Marvin Gillman.

Surgery of the Eye, a full-time course, Oct. 28 through Nov. 2, given under the direction of Dr. Rudolf Aebli.

Ophthalmoscopy, a part-time course, Nov. 4 through 8, given under the direction of Dr. George N. Wise.

Surgery of the Cornea, a full-time course, Dec. 2 through 6, given under the direction of Dr. Ramon Castroviejo.

For further information concerning these and other courses offered by the department of ophthalmology during each academic year write to Office of the Associate Dean, New York University Post-Graduate Medical School, 550 First Ave., New York 16.

GENERAL NEWS

Eye Hospital of Shikarpur.—Dr. Roland I. Pritikin, while at Shikarpur, West Pakistan, earlier this year, was named President of the Henry Holland Hospitals Alumni Association and of the Henry Holland Mission Hospitals Fund.

All alumni of the Eye Hospitals of Shikarpur and Khairpur Mirs are urged to remit an annual subscription of $1.00 or more to Dr. Victor E. Lepisto, Treasurer, 238 Quincy St., Hancock, Mich. Dr. Derrick Vail is honorary chairman of the Board of Trustees of the Alumni and Fund.

New Eye Clinic, Temple University Medical Centers.—A large group of Philadelphia-area ophthalmologists attended a special program and open house to dedicate the new eye clinic of the Department of Ophthalmology, March 6, at the Temple University Medical Center.

One of the nation's leading specialists, Dr. Algernon B. Reese, Chairman of the Section on Ophthalmology of the American Medical Association, addressed the meeting on surgery for the relief of cataract. Dr. Reese, an authority on eye surgery, is also Clinical Professor of Ophthalmology of the College of Physicians of Surgeons of Columbia University in New York.

Dr. Robert Robbins, Professor of Radiology and Director of the Radiotherapy Department at Temple University Medical Center, spoke on irradiation of the eye.

Under the direction of Dr. Glen G. Gibson, Professor and Head of the Department of Ophthalmology, the clinic includes all the modern diagnostic instruments. Special operating room equipment for the performance of eye surgery also has been obtained.

Discontinuation of Medical Book Shipments to Korea.—The American-Korean Foundation and the United States Army Medical Service have announced the discontinuation of their joint project of shipping medical books contributed by individual physicians, medical schools, hospitals, and state and local medical societies to Korea.

Books should not be sent to the Sharpe General Depot in California as in the past, for facilities no longer exist for packing and transshipping to Korea.

In making the announcement, Howard A. Rusk, M.D., President, American-Korean Foundation, said, "The response of physicians and medical groups throughout the country for our appeal for books for Korean medical schools has been so generous that further contributions are not needed." As a result of this program, Dr. Rusk stated, over 77 tons, valued at $76,000, of medical texts, references, and periodicals have been shipped to Korea for distribution to Korean medical schools.

Contribution for Research in Eye Diseases.—A most significant and generous contribution for research in the diseases of the eye has been given to the University of Toronto by Herbert G. Stapells, Q. C., Toronto corporation lawyer.

His donation of $25,000 will be used for clinical research by members of the staff of the Department of Ophthalmology in the University's teaching hospitals and also to defray expenses of staff members for short periods of study in other research centers.

The Department has received large support from government sources for its eye research program, but few private persons have supported clinical eye research to such an extent.

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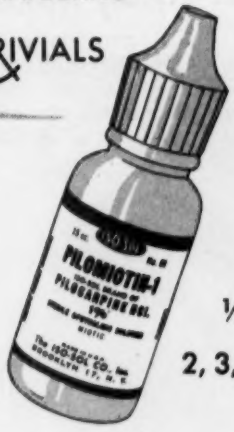

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The Eighth Annual meeting of the New Orleans Academy of Ophthalmology will be held in New Orleans in the Roosevelt Hotel—February 24-28, 1958, featuring "Symposium on Uveitis." The registration fee of $75.00 includes associate membership in the Academy for the year 1958, as well as all other features of the convention. Hotel reservations should be made early by writing directly to the Executive Secretary, P. O. Box 469, New Orleans, La.

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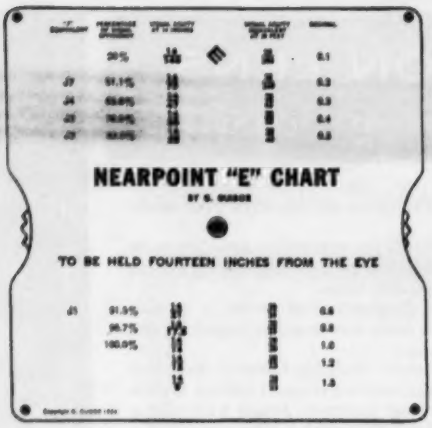

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4-12-55: Right vision with above CATAREX T lens = 20/40+. Manifest O.D. +10.50Dsph. ○ +1.50Dcyl. ax 105 = 20/15+; +2.75D add = Jg. 0.75 @ 13". Patient was allowed to retain first CATAREX T lens until second pair was received with new Rx.

5-5-55: Right vision with 4-12-55 Rx = 20/20. Manifest O.D. +10.00Dsph. ○ +1.50Dcyl. ax 105 = 20/15+. Again, patient was allowed to retain former lens until the new Rx in CATAREX T was ready.

5-31-55: Right vision with 5-5-55 Rx = 20/50. Manifest O.D. +10.00Dsph. ○ +1.00Dcyl. ax 60 = 20/15+. Rx Right: Manifest findings in CATAREX T. Left: lens to balance.

7-6-55: Right vision with 5-31-55 Rx = 20/20+. Manifest O.D. +10.00Dsph. ○ +1.00Dcyl. ax 75 = 20/15+. Rx Right: Manifest findings in CATAREX T. Left: lens to balance.

7-27-55: Manifest O.D. +10.50Dsph. ○ +1.25Dcyl. ax 90 = 20/15+; +2.75D add = Jg. 0.75 @ 13¾". Rx Right: CATAREX D (permanent). Left: lens to balance.

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